RETURN TO H. W. HOWARD

RECEIVED
SEP 14 1959
H. W. H.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

VOLUME 82, ART. 1 PAGES 1–190

Editor in Chief
OTTO V. ST. WHITELOCK

Managing Editor
FRANKLIN N. FURNESS

Associate Editors
PHILIP RESSNER, PETER A. STURGEON

RECENT CONTRIBUTIONS TO ANTIBACTERIAL THERAPY

LIST OF AUTHORS

PAUL S. RHOADS (*Conference Chairman*), W. G. ANLYAN, R. E. BAGDON, F. T. BECKER, G. L. BECKER, O. C. BEYER, S. BIELINSKI, S. M. BLUEFARB, W. P. BOGER, A. BORGSTEDT, M. M. CAHN, A. D. CALABRESE, C. W. DAESCHNER, W. F. DELORENZO, J. W. DRAPER, P. DRUCKER, E. EDELSON, J. C. ELIA, A. B. FALK, S. M. FINEGOLD, J. FINKEL, C. FLANIGAN, JR., R. D. FLOYD, J. M. FOX, J. J. GAVIN, J. GELB, N. GEORGIADE, D. B. GERSHENFELD, W. J. GRACE, E. GRUNBERG, S. L. HANFLING, H. O. KENDALL, W. S. KISER, Z. KUDINOFF, V. E. KVINGE, W. A. LEFF, B. H. LEMING, JR., E. J. LEVY, S. W. LEVY, J. J. MCDONOUGH, T. D. MICHAEL, G. A. MOORE, F. MORRIS, T. V. MORTON, N. MULLA, K. PICKRELL, L. O. RANDALL, L. E. SAVEL, R. J. SCHNITZER, M. SIERP, L. E. SKINNER, E. H. TOWNSEND, JR., J. L. TUURA, P. L. WILLIAMS, AND J. D. YOUNG

Consulting Editor
SARAH R. GUSTAFSON

NEW YORK

PUBLISHED BY THE ACADEMY

September 1, 1959

THE NEW YORK ACADEMY OF SCIENCES

(Founded in 1817)

COUNCIL, 1959

President
HILARY KOPROWSKI

President-Elect
M. J. KOPAC

Vice-Presidents
LYLE BORST
C. P. RHOADS

Recording Secretary
EMERSON DAY

Corresponding Secretary
FREDERICK Y. WISELOGLE

Treasurer
GUSTAV J. MARTIN

Elected Councilors

1957–1959
GEORGE H. MANGUN
MINA REES
HAYDEN C. NICHOLSON
WILLIAM W. WALCOTT

1958–1960
DAVID A. KARNOFSKY
WAYNE W. UMBREIT
GUSTAV J. MARTIN
JOHN E. VANCE

1959–1961
JOHN E. DEITRICK
ROBERT S. MORISON
CHARLES W. MUSHETT
E. L. TATUM

Finance Committee
HARDEN F. TAYLOR, *Chairman*
GORDON Y. BILLARD
ROBERT F. LIGHT

Executive Director
EUNICE THOMAS MINER

SECTION OF BIOLOGICAL AND MEDICAL SCIENCES
ROBERT L. KROC, *Chairman*
CHARLES NOBACK, *Vice-Chairman*

DIVISION OF ANTHROPOLOGY
DOROTHY L. KEUR, *Chairman*
DOROTHY CROSS JENSEN, *Vice-Chairman*

DIVISION OF INSTRUMENTATION
DUNCAN A. HOLADAY, *Chairman*
ANDRES FERRARI, *Vice-Chairman*

DIVISION OF MYCOLOGY
KARL MARAMOROSCH, *Chairman*
EMANUEL GRUNBERG, *Vice-Chairman*

DIVISION OF PSYCHOLOGY
GREGORY RAZRAN, *Chairman*
LOUIS W. MAX, *Vice-Chairman*

SECTION OF CHEMICAL SCIENCES
KARL FOLKERS, *Chairman*
FREDERICK R. EIRICH, *Vice-Chairman*

SECTION OF GEOLOGICAL SCIENCES
KURT LOWE, *Chairman*
FREDERICK P. YOUNG, *Vice-Chairman*

DIVISION OF OCEANOGRAPHY AND METEOROLOGY
ABRAHAM S. KUSSMAN, *Chairman*
CHARLES KNUDSEN, *Vice-Chairman*

SECTION OF PHYSICAL SCIENCES
EMANUEL R. PIORE, *Chairman*
E. BROMBERG, *Vice-Chairman*

DIVISION OF ENGINEERING
THOMAS B. DREW, *Chairman*

Past Presidents
WILLIAM K. GREGORY
VICTOR K. LAMER
HORACE W. STUNKARD
M. L. CROSSLEY
ROSS F. NIGRELLI
HARDEN F. TAYLOR
BORIS PREGEL

The Sections and the Divisions hold meetings regularly, one evening each month, during the academic year, October to May, inclusive. All meetings are held at the building of The New York Academy of Sciences, 2 East Sixty-third Street, New York 21, New York.

Conferences are also held at irregular intervals at times announced by special programs.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

VOLUME 82, ART. 1 PAGES 1–190

September 1, 1959

RECEIVED
SEP 14 1959
H. W. H.

Editor in Chief

OTTO V. ST. WHITELOCK

Managing Editor

FRANKLIN N. FURNESS

Associate Editors

PHILIP RESSNER PETER A. STURGEON

Consulting Editor

SARAH R. GUSTAFSON

RECENT CONTRIBUTIONS TO ANTIBACTERIAL THERAPY*

CONTENTS

* This series of papers is the result of a conference on *Recent Contributions to Antibacterial Therapy* held by The New York Academy of Sciences on May 21 and 22, 1959.

Copyright, 1959, by the New York Academy of Sciences

PHARMACOLOGICAL STUDIES WITH SULFADIMETHOXINE

R. E. Bagdon, L. O. Randall
Hoffmann-La Roche Inc., Nutley, N. J.

W. A. Leff
Kessler Institute for Rehabilitation, West Orange, N. J.

Earlier investigations have shown sulfadimethoxine (Madribon*) to be a potent antibacterial agent. High chemotherapeutic activity was exhibited by this drug toward experimentally induced infections in animals and clinically in the treatment of various diseases of infectious origin.[1-3] Following oral administration of sulfadimethoxine to rats, high blood and tissue levels were rapidly attained, and the drug was excreted slowly by the kidneys over a period of several days.[4] In man, Brandman *et al.* demonstrated that sulfadimethoxine also remained at high concentrations in the blood and urine for an extended period; measurable amounts of drug were detected in the blood 4 days after administration.[5] Chronic toxicity experiments of 3 months' duration with dogs and rats indicated that sulfadimethoxine exerts a low toxicity.[4]

A low incidence of untoward reactions is particularly important when a drug having a prolonged duration of action is employed clinically. Therefore, tolerance studies in animals and man were extended to obtain additional information about potential side effects following chronic administration of sulfadimethoxine. The results of these investigations are presented in this paper.

Methods

Sulfadimethoxine was incorporated in the diet and administered to 20 male and female Sprague-Dawley rats. Another group of 20 rats served as controls. The animals were maintained on ground Purina Chow pellets ad libitum. After 11 weeks of treatment the rats were paired and bred to obtain a first generation. After weaning, rats comprising the first generation were also given the drug as a dietary admixture. The parent and first generations have received sulfadimethoxine continuously in the diet for 34 and 19 weeks, respectively.

Sulfadimethoxine was determined in tissues and body fluids by the method of Bratton and Marshall.[6] Hematological determinations, including total and differential leukocyte counts, hematocrit, and hemoglobin, were performed on the parent generation at the tenth experimental week. Oxygen consumption of surviving liver and kidney slices was determined by conventional manometric methods; Krebs-Ringer phosphate buffer with the calcium concentration reduced to one half was used in these measurements.[7] The tissue slices were rapidly prepared and placed in the main compartment of Warburg flasks containing cold buffer solution. The flasks were gassed with 100 per cent oxygen and incubated with shaking at 37.5° C. for 30 min. Readings were made at 30-min. intervals over a 2-hour period. Results were expressed as QO_2 = μl. O_2 taken up per milligram wet weight of tissue. Serum glutamic-pyruvic trans-

* Hoffmann-La Roche.

aminase levels were determined spectrophotometrically.[8] Estimations of the cecal bacterial flora were made, using plain and differential culture media.

Clinical observations were made in 35 paraplegic patients who were afebrile and had not shown signs of acute bladder flare-up for at least 2 months prior to receiving sulfadimethoxine as prophylactic therapy.[9] Most of these patients were engaged in a rehabilitation program designed for paraplegics. All received an initial loading dose of 1 gm. of the drug daily for the first 3 days and then were maintained on a daily dose of 0.5 gm. for more than 1 year. When diagnostic procedures such as cystoscopy, intravenous and retrograde pyelograms, or treatment for decubitus ulcers were required, the dosage of sulfadimethoxine was increased twofold for a few days. Complete hemograms were

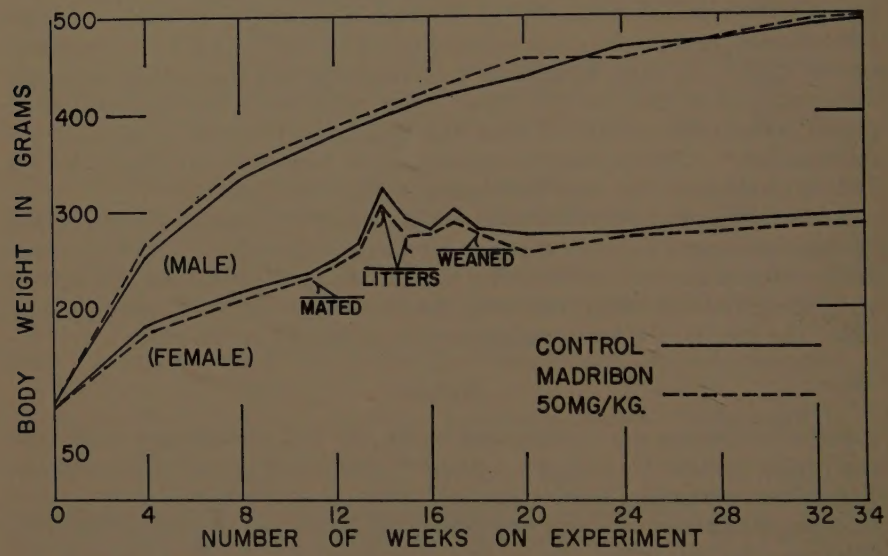


FIGURE 1. Growth curves of parent-generation rats that received sulfadimethoxine (50 mg./kg.) in the diet for 34 weeks.

performed on all patients every 10 days during the first 6 months of the clinical study and at frequent intervals thereafter. Urine cultures with sensitivity tests were done weekly on all patients during the initial 6 months of therapy.

Results

Ten male and 10 female rats of the Sprague-Dawley strain were administered sulfadimethoxine (50 mg./kg.) continuously for 34 weeks. One male control rat expired at the twenty-second experimental week, and another male in the treatment group succumbed during the twenty-seventh week. These deaths were attributed to pneumonia and are unrelated to the administration of the drug. The health of the remaining animals has been optimal during the entire experimental period. The average weekly body weights of the parent generation are shown in FIGURE 1. The rates of growth, activity, food consumption, and general condition have not been adversely influenced, and these rats have

not exhibited signs of toxicity. The lack of an effect on growth supports the conclusion that higher doses of sulfadimethoxine are required to exert goitrogenic activity in this species.

Complete hematological determinations, including measurements of hematocrit, hemoglobin, and total and differential leukocytes were performed during the tenth experimental week; these results are shown in TABLE 1. Sulfadimethoxine had no deleterious effects on circulating blood cells or hemopoietic organs and tissues.

After 11 weeks of treatment the rats were paired and bred to obtain a first generation. These data provide information concerning the influence of sulfa-

TABLE 1

AVERAGE BLOOD COUNTS OF PARENT GENERATION RATS GIVEN SULFADIMETHOXINE (50 MG./KG.) FOR 10 WEEKS

Group	No. and sex of rats	WBC in thousands	Hematocrit per cent vol. RBC	Hb in gm./100 ml.	Differential							Per cent Nucl. RBC
					NSN	SN	L	M	E	B	Pl. cells	
Sulfadimethoxine	10 Females	10.9	46.2	14.8	0	7.6	89.6	1.7	1.1	0.0	0.0	0
Sulfadimethoxine	10 Males	18.7	46.4	14.7	0	8.0	89.3	1.7	0.9	0.1	0.0	0
Controls	10 Females	13.7	46.6	15.2	0	10.9	86.4	1.4	1.0	0.1	0.2	0
Controls	10 Males	16.2	46.9	15.0	0	11.2	85.5	1.6	1.5	0.2	0.0	0

TABLE 2

INFLUENCE OF SULFADIMETHOXINE ON REPRODUCTION

Sulfadimethoxine (50 mg./kg.) for 11 weeks

No. females bred	Litters obtained		Days to parturition	No. per litter	Survivors at weaning	Wt. (gm.) at weaning (21 days)
10	9	Av. of 8 rats*	26	9	6	45
			Controls			
10	10	Av. of 10 rats	26	10	8	42

* One female devoured her litter.

dimethoxine on fertility, pregnancy, lactation, and growth of the newborn; the results of these experiments are recorded in TABLE 2. The absence of congenital malformations, absorption of fetuses, or other abnormalities indicates that chronic administration of this drug does not exert deleterious effects on the process of reproduction.

After weaning, rats constituting the first generation were given sulfadimethoxine (50 mg./kg.) for 19 weeks, and mortality or signs of toxicity have not occurred. In the corresponding group of controls 3 rats contracted a severe respiratory infection and expired during the ninth to thirteenth experimental weeks. The body weights of the first-generation rats at weekly intervals are shown in FIGURE 2; these animals have exhibited a normal rate of growth.

At the sixth experimental week, 6 rats were sacrificed and the levels of drug in blood and various tissues determined. In these measurements, material that reacted directly with the Bratton-Marshall reagents was termed free or unbound drug. This material represents all compounds containing a free N^4 aminophenyl group, including the glucuronide conjugate. Metabolites that required acid hydrolysis prior to analysis were taken to be acetylated or bound drug; these results are shown in TABLE 3. Each value represents the average of duplicate determinations performed in 6 rats. Prolonged administration of

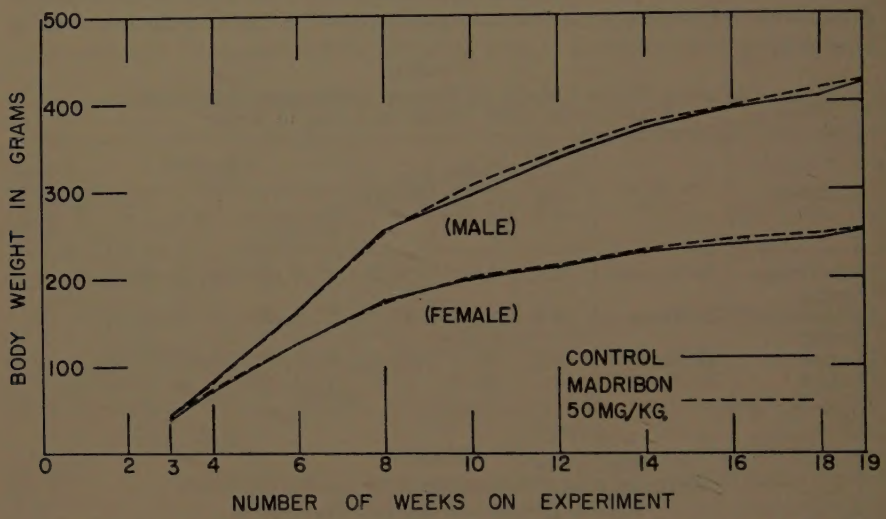


FIGURE 2. Growth curves of first-generation rats that received sulfadimethoxine (50 mg./kg.) in the diet for 19 weeks.

TABLE 3

FIRST GENERATION RATS GIVEN SULFADIMETHOXINE (50 MG./KG.) FOR 6 WEEKS

Levels of drug in blood and tissues (mg. per cent)

	Blood	Kidneys	Liver	Muscle	Brain
Unbound	13.70	3.60	2.70	1.61	0.78
Bound	0.90				

sulfadimethoxine did not result in an excessive accumulation of the drug in blood and tissues. These concentrations of drug are not significantly different from the blood and tissue levels achieved in rats after 4 successive daily doses of sulfadimethoxine.[4] These findings indicate that the rat excretes excessive amounts of the drug, and in this manner abnormal amounts of sulfonamide are prevented from accumulating in the tissues.

At the eighth experimental week groups of 6 treated and 6 control rats were sacrificed, and cultures of the cecal contents were examined to determine if alterations of the normal bacterial flora had occurred.* *Escherichia coli* flora

* These determinations were performed by E. Grunberg.

were found to be diminished by administration of sulfadimethoxine when compared with controls; cultures taken from the cecal contents of 4 of the 6 control rats exhibited a heavy growth of the organism, in contrast to 1 rat in the group of 6 sulfadimethoxine-treated animals. Sulfadimethoxine had no effect against *Streptococcus fecalis* or other bacterial flora normally present in the intestinal tracts of rats.

Despite long-term administration of sulfadimethoxine, evidence of hepatic or renal damage has not been detected. In addition to histological examination of tissue sections,[4] selected biochemical measurements were made to ascertain if changes in cellular metabolism had been produced by the drug.

The serum glutamic-pyruvic transaminase (SGP-T) levels of 4 rats given sulfadimethoxine for 10 weeks remained within normal limits. Elevations of this enzyme have been shown to reflect hepatocellular injury.[10] Another group of 4 rats from the first generation given the drug continuously for 10 weeks was sacrificed together with 4 control animals, and the oxygen consumption of surviving liver and kidney slices was determined by manometric methods. The average QO_2 of liver and kidney slices of control rats was found to be 1.1 and 2.3, respectively; similar values of 0.7 and 2.1 were obtained, using liver and kidney slices of rats receiving the drug over an extended interval. These results indicate that chronic administration of high doses of sulfadimethoxine to rats does not significantly impair endogenous respiration of liver and kidney tissue.

Sulfadimethoxine has been given continuously to a group of 35 paraplegics with spinal cord bladder for as long as one year to investigate its effectiveness as a prophylactic and therapeutic agent in the management of chronic cystitis. Urinary tract infections are relatively common complications of paraplegia as a consequence of urine stasis caused by a hypotonic bladder. The patients were given an initial loading dose of 1 gm. of sulfadimethoxine and then were maintained on a single daily dose of 0.5 gm. Urine specimens were obtained weekly, and cultures with sensitivity tests were done during the initial 6-month period. The weekly urine cultures revealed the same spectrum of organisms (*E. coli*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*) as was found prior to treatment with sulfadimethoxine, and these organisms showed a complete resistance to this sulfonamide *in vitro*. However, none of the patients given sulfadimethoxine as a prophylactic measure exhibited the clinical signs of bladder infection. Another patient who was receiving tetracycline had a recurrence of bladder infection with fever of 102 to 103° F., chills, and general malaise. He was given 1 gm. of sulfadimethoxine twice a day for 2 days and 0.5 gm. daily thereafter. The clinical manifestations subsided in 24 hours and he has continued to be asymptomatic. These results indicate that *in vitro* sensitivity tests should not be relied upon as an indication of clinical effectiveness.

Every patient in this investigation tolerated the drug without the occurrence of blood dyscrasias or neurological, renal, gastrointestinal, or allergic reactions. The complete absence of side effects in these patients despite the extended period of treatment was a particularly impressive finding of this clinical study.

Discussion. Pharmacological and toxicological investigations of sulfadimethoxine indicate that this drug is a superior chemotherapeutic agent. Fol-

lowing oral administration, high blood and tissue levels of the drug are attained, and the drug is slowly excreted by the urinary route.

Chronic administration of sulfadimethoxine to animals and man has not produced the serious toxic manifestations often encountered with the use of sulfadiazine and other sulfonamides.[11, 12] In the present study, blood dyscrasias, renal complications, hepatitis, dermatological manifestations and other hypersensitivity reactions, or involvement of the central and peripheral nervous system were not detected despite the long duration of treatment. The absence of renal obstruction and other urinary tract reactions was not unexpected, since Koechlin *et al.* have demonstrated that sulfadimethoxine is excreted by humans largely as a highly soluble glucuronide.[13] The lack of deleterious actions on tissues and blood cells of the host is a distinct advantage exhibited by sulfadimethoxine over other antibacterial sulfonamides.

Summary

A parent generation of 20 rats was administered sulfadimethoxine (50 mg./kg.) for 34 weeks without the occurrence of toxic manifestations. After 11 weeks of treatment the rats were bred, and the litters obtained have also been maintained on the drug continuously for 19 weeks. Chronic administration of sulfadimethoxine to rats did not adversely affect growth, activity, general condition, food consumption, or the process of reproduction. Evidence of renal or hepatic injury was not observed, and complete hematological determinations did not reveal any abnormalities of the circulating blood cells or hemopoietic tissues. Examination of the cecal bacterial flora of rats of the first generation after 8 weeks of treatment revealed the facts that the *E. coli* were markedly reduced as compared to untreated controls, but that other intestinal flora were unaffected.

Sulfadimethoxine has been given continuously to a group of 35 paraplegics for over 1 year in a daily maintenance dose of 0.5 gm. to investigate the effectiveness as a prophylactic and therapeutic agent in the management of chronic cystitis. The complete absence of side effects in these patients was particularly impressive. The low toxicity exhibited by sulfadimethoxine in these animal and clinical investigations indicates that this drug is a superior antibacterial sulfonamide.

References

1. Semenitz, E. 1954. Ergebnisse der bacteriologischen Pruefung zweier neuen Sulfonamide. Z. Immunitaetsforsch. **3:** 388.
2. Schnitzer, R. J., W. F. DeLorenzo, E. Grunberg & R. Russomanno. 1958. Chemotherapeutic studies with 2,4-dimethoxy-6-sulfanilamido-1,3-diazine. Proc. Soc. Exptl. Biol. Med. **99:** 421.
3. Fust, B. & R. Boehni. 1959. Tolerance and antibacterial properties of 2,4-dimethoxy-6-sulfanilamido-1,3-diazine and some other sulfonamides. Antibiotic Med. & Clin. Therapy. **6:** 3.
4. Randall, L. O., R. E. Bagdon & R. Engelberg. 1959. Toxicological and metabolic studies on (2,4-dimethoxy-6-sulfanilamido-1,3-diazone) Madribon. J. Toxicol. & Appl. Pharmacol. **6:** 3.
5. Brandman, O., C. Oyer & R. Engelberg. 1959. Blood levels and urinary excretion of a long acting sulfonamide, Madribon, in man. J. Med. Soc. New Jersey. **56:** 24.
6. Bratton, A. C. & E. K. Marshall. 1939. A new coupling component for sulfanilamide determination. J. Biol. Chem. **128:** 537.

7. Umbriet, W. W., R. H. Burris & J. F. Stauffer. 1957. Manometric Techniques. : 149. Burgess. New York, N. Y.
8. Wróblewski, F. & J. S. LaDue. 1956. Serum glutamic pyruvic transaminase in cardiac and hepatic disease. Proc. Soc. Exptl. Biol. Med. **91:** 569.
9. Leff, W. A. 1959. A clinical study with sulfadimethoxine (Madribon) in cystitis associated with paraplegia. Antibiotic Med. & Clin. Therapy. **6:** 44.
10. Wróblewski, F. & J. S. LaDue. 1956. Serum glutamic pyruvic transaminase in hepatic disease. A preliminary report. Ann. Intern. Med. **45:** 801.
11. Van Dyke, H. B. 1943. The toxic effects of sulfonamides. Ann. N. Y. Acad. Sci. **44**(5): 447.
12. Kutscher, A. H., S. L. Laud & R. Segall. 1954. The clinical toxicity of antibiotics and sulfonamides; a comparative review. J. Allergy. **25:** 135–150.
13. Koechlin, B., W. Kern & R. Engelberg. 1959. A comparative study of the metabolism and the urinary excretion of 2,4-dimethoxy-6-sulfanilamido-1,3-diazine (Madribon). Antibiotic Med. & Clin. Therapy. **6:** 22.

COMPARATIVE CHEMOTHERAPEUTIC STUDIES WITH THE NEWER SULFONAMIDES

W. F. DeLorenzo and R. J. Schnitzer
Chemotherapy Laboratory, Hoffmann-La Roche Inc., Nutley, N. J.

In a recent study Fust and Boehni have described similarities and differences of the activity of nine sulfonamides.[1] Owing to the chemical relationships of the sulfonamides, their chemotherapeutic efficacy is bound to be similar in experimental tests in which their activity against pathogenic organisms is evaluated. Nevertheless, the history of the sulfonamides and the development of new compounds of this class during recent years has brought forth evidence that different sulfonamides possess different biological properties that can influence their antibacterial qualities. It has long been known that the activity of sulfonamides in infections with various organisms is quantitatively different and that these differences are, to a certain degree, determined by the fate of the drugs in the host organisms; that is, their absorption, distribution, and elimination. The most important quality is, however, the antibacterial activity as such, and it is this property that has been studied in the following experiments in which a comparison of four of the more recently developed sulfonamides has been attempted. Only *in vivo* experiments are presented and discussed.

The following 4 sulfonamides tested (FIGURE 1) were selected on the basis of different pharmacological characteristics: Madribon* (SDM), Gantrisin* (ST), Kynex† (SMP), and Orisul‡ (SP).

A quantitative evaluation in infections with representative Gram-positive and Gram-negative organisms is shown in TABLE 1.

The data in TABLE 1 are based on experiments in mice carried out by the methods described earlier,[3, 5] which consist in the single or repeated oral treatment of intra-abdominal infections with approximately 1000 MLD of the different organisms. In all instances where the natural pathogenicity of the bacteria is low, such as staphylococci, salmonellae, shigellae, *Escherichia coli*, or pseudomonas, the conditioning of mice with gastric mucin was employed. The CD_{50} as given in the table was calculated according to Reed and Muench[9] on the basis of survival at the end of a 3-week observation period.

The data in TABLE 1 indicate that these four sulfonamides may differ considerably in their activity toward the various test organisms. Apparently independent of their pharmacological properties, their activity seems to be determined rather by the sensitivity of the different organisms or the character of the infection produced. Although long-acting sulfonamides such as SDM and SMP may exert very marked activity in all infections tested, SMP was, in 2 infections (streptococci and *Salmonella schottmülleri*), 5 or 6 times more active. On the other hand, the differences of activity between SDM and SI were not too great in the majority of instances, with the exception of pneumococci and pseudomonas. SP occupies a particular position in this group of

* Hoffmann-La Roche.
† Lederle.
‡ Ciba (Basel, Switzerland).

compounds on account of a certain specificity in the infections with Gram-positive organisms.[7] Its CD_{50} in streptococci and staphylococci was within the range of those obtained with SDM and SI; in pneumococci it was superior to the latter. In all infections with Gram-negative bacteria higher doses were required than of the three other compounds.

Nevertheless, a certain degree of similarity also governs this accumulation of different values. In all instances streptococci and staphylococci were the

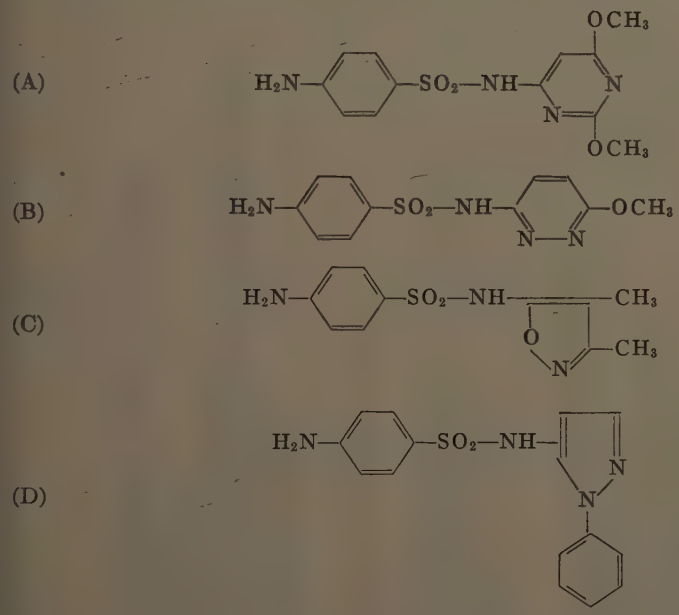


FIGURE 1. Structures of the four sulfonamides investigated: (A) 2,4-dimethoxy-6-sulfanilamido-1,3-diazine (sulfadimethoxine, SDM, Madribon[1-4]); (B) 3-sulfanilamido-6-methoxypyridazine (sulfamethoxypyridazine, SMP, Kynex[1-6]); (C) 5-sulfanilamido-3,4-dimethylisoxazole (sulfisoxazole, SI, Gantrisin[1, 5]); (D) 3-sulfanilamido-2-phenylpyrazole (sulfaphenazole, SP, Orisul[1, 7, 8]).

TABLE 1

In Vivo ACTIVITY OF SULFONAMIDES AGAINST VARIOUS BACTERIAL INFECTIONS

Organism	No. of doses	CD_{50}: mg./kg.			
		SDM	SI	SMP	SP
Streptococcus hemolyticus No. 4	6	78.5	106.0	15.2	62.0
Diplococcus pneumoniae No. 6301	6	211.0	1000.0	366.0	595.0
Staphylococcus aureus Smith	4	53.2	68.3	—	90.1
Salmonella typhosa P58a	1	10.8	24.1	6.1	54.0
Salmonella schottmülleri	1	91.4	125.0	16.5	369.5
Shigella flexneri	4	99.5	112.0	56.3	235.0
Escherichia coli J	4	88.9	67.8	—	159.0
Klebsiella pneumoniae	6	71.7	119.0	—	—
Pseudomonas aeruginosa B	4	325.0	582.0	162.0	>500.0

more sensitive bacteria of the Gram-positive organisms, *Salmonella typhosa* was always more sensitive than other members of the *coli-Shigella-Salmonella* group, whereas *Pseudomonas aeruginosa* responded only to comparatively high doses of all sulfonamides.

It is not without interest that a very similar pattern has been observed in the experiments of Fust and Boehni,[1] which were carried out with different strains and sometimes even with an entirely different technique (that is, with staphylococci) and is shown in FIGURE 2.

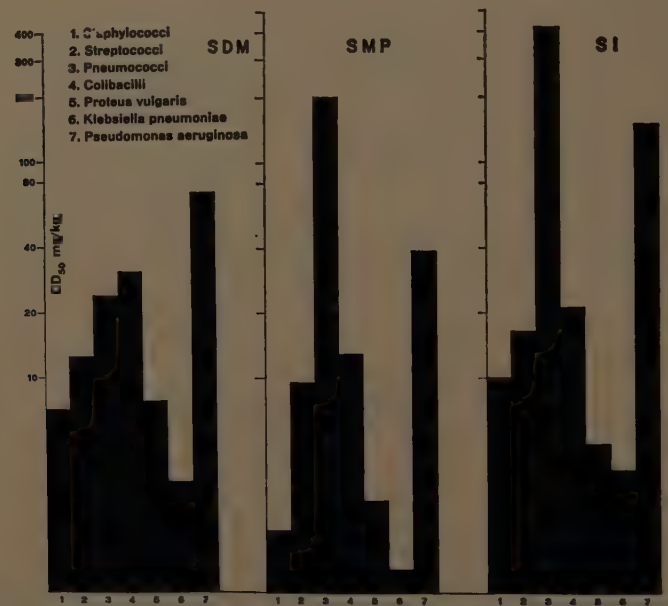


FIGURE 2. Equieffective doses of 3 sulfonamides against infections with 3 Gram-positive and 4 Gram-negative bacteria. Reproduced by permission from *Antibiotics and Chemotherapy*.[1]

One can readily recognize the generally higher sensitivity of the members of the enteric group of organisms and the lower response of pneumococci (most marked in SMP and SI) and pseudomonas.

In the previous publication on antibacterial sulfonamides by The New York Academy of Sciences, Domagk[10] pointed out that the evaluation of a chemotherapeutic agent should be based on the ratio of the tolerated to the effective dose. In other words, Ehrlich's principle of the chemotherapeutic index should be applied also to the sulfonamides, thus correlating the toxicological and the antibacterial aspects. Such ratios, namely, LD_{50}/CD_{50}, both based on oral drug administration in mice, are shown in TABLE 2.

The values of these ratios are influenced by the degree of toxicity, which appears in increasing order as SDM < SI < SMP = SP.

In agreement with the CD_{50} of the sulfonamides, the maxima of the ratios were in all instances obtained in experiments with *S. typhosa*; the minima were

found in the pneumococcal infection, with the exception of SDM, where it was derived from the pseudomonas experiment, although both SI and SP had a higher CD_{50} in this infection. Owing to its particularly low toxicity and high activity, SDM showed the highest ratios.

Notwithstanding the general similarity of the biological properties of the four sulfonamides compared here, it is possible to show that they belong in two distinct groups, as shown in TABLE 3.

The sulfonamides of longest half life have also identical average values of activity, and the same applies to the drugs with shorter persistence in the blood. The half life, however, seems not to be the only factor responsible for the anti-

TABLE 2

ACUTE ORAL TOXICITY IN MICE AND RATIOS LD_{50}/CD_{50} OF 4 SULFONAMIDES

Compound	LD_{50} mg./kg.	Ratio LD_{50}/CD_{50}	
		maximum	minimum
Sulfadimethoxine (SDM)	>16,000	>1481	>49
Sulfisoxazole (SI)	7,500	311	7
Sulfamethoxypyridazine (SMP)	2,500	410	7
Sulfaphenazole (SP)	2,500	46	4

TABLE 3

COMPARISON OF HALF LIFE, TOXICITY, AND ACTIVITY OF 4 SULFONAMIDES

Compound	Half life* (hours)	LD_{50} mg./kg.	Average CD_{50}† mg./kg.
Sulfadimethoxine	33‡	>16,000	114
Sulfamethoxypyridazine	44§	2,500	104
Sulfaphenazole	9–10‖	2,500	258
Sulfisoxazole	6–7§	7,500	245

* In blood and serum of humans after 2.0 gm. of drug.
† In 6 to 9 infections.
‡ According to E. Gans (personal communication).
§ Calculated (by Struller) from Finland *et al.*[12]
‖ Calculated (by Struller) from Rentchnick.[13]

bacterial activity, because the difference in the half lives of the two groups is fourfold to sevenfold, while the difference in average activity is approximately twofold. Moreover, the toxicity of the compounds introduces still another factor of differentiation, resulting in a different aspect of each of the four sulfonamides compared.

On the basis of half life, one might arrange the compounds in the order SMP > SDM > SP > SI; according to toxicity, SDM < SI < SMP = SP; whereas activity shows the grouping SDM = SMP > SI = SP.

Comparatively small differences of activity can be correlated, therefore, with marked differences of half life and toxicity, thus indicating that the degree of antibacterial effect is, as stated earlier,[8] an intrinsic property of the sulfonamides.

It should be pointed out here that we have discussed laboratory findings. Other considerations might enter into practical medical situations; properties of drugs that do not appear in the experiment in mice might determine their clinical selection, and the desired activity can always be obtained with different drugs by the adjustment of size of dose and frequency of administration.

We have used the expression antibacterial activity so often in the preceding parts of this paper that we believe we are justified in writing at least a few words about the type of activity that has been observed in our experiments. Although most of these experiments have been carried out only with sulfadimethoxine, no claim is made that the findings represent a specific property of this drug. We have some, though not extensive, experience that other sulfonamides act, if not in an identical manner, then at least similarly.

Schnitzer and DeLorenzo[11] have demonstrated that the activity of SDM in the *S. typhosa* infection of mice could not be antagonized by an excess of para-

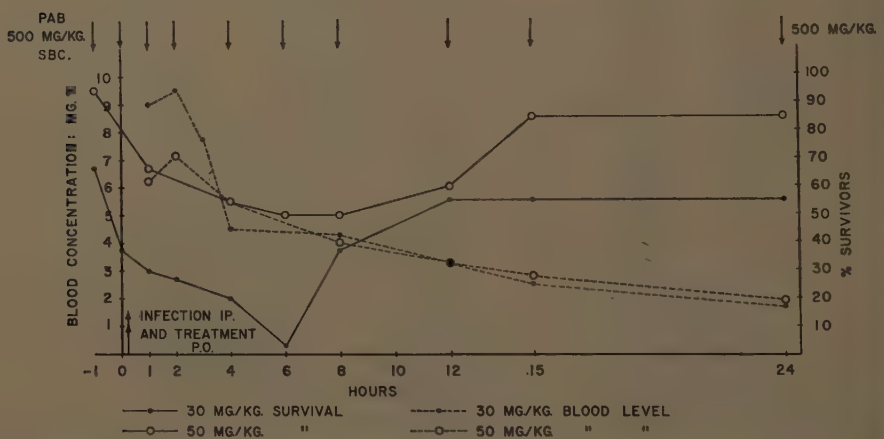


FIGURE 3. The effect of para-aminobenzoic acid (PAB) on the activity of SDM in *S. typhosa* infection of mice.

aminobenzoic acid (PAB) after 8 to 12 hours, although the drug concentration in the blood, and perhaps also the tissues, was declining at that time; this is shown in FIGURE 3.

Ten groups of mice uniformly infected with 1000 MLD of *S. typhosa* P58a and treated once with SDM 30 mg./kg. or 50 mg./kg. orally received a subcutaneous injection of 500 mg. PAB at 2-hour intervals. The survival rate of the different groups of animals after the usual 20-day observation time shows that maximal inhibition occurred at the 6-hour interval when the blood level was still comparatively high, but that after 8 to 15 hours the antagonistic effect decreased to an insignificant level. This finding was interpreted by the assumption that at this time the drug effect on the bacterium had become irreversible.

It was possible to demonstrate that the higher dose of SDM, namely, 50 mg./kg., indeed produced an irreversible damage to the infective organisms.

Such an experiment is presented in FIGURE 4. An intra-abdominal infection with 1000 MLD of *S. typhosa* P58a was treated once with 50 or 200 mg./kg.

SDM orally. Besides groups of 10 mice that were observed for 14 days (the solid lines of the graph), 5 mice of the 4 groups were sacrificed at the intervals indicated in the graph. Cultures on agar containing 0.2 per cent PAB were taken from the site of infection and the heart blood. The symbols in the graph, in which every block represents 5 mice, show that, regardless of the treatment, the *Salmonella* septicemia had been established after 6 hours. After 12 to 24 hours, depending on the drug dose, *Salmonella* could no longer be demonstrated in the blood and in the peritoneal cavity, with the exception of a few scattered colonies in occasional mice. The animals were sterile after 48 hours and remained so after 5 and 10 days, when similar examinations of survivors were done. The 100 per cent survival rate confirms these observations.

Another of our assumptions was the possible influence of the host's defense mechanism in support of the direct chemotherapeutic effect.

We attempted to demonstrate this by including in an experiment identical with the one above, a group of animals that had received a total of 5 mg. cortisone acetate distributed over 3 days. FIGURE 5 shows that the conditioning

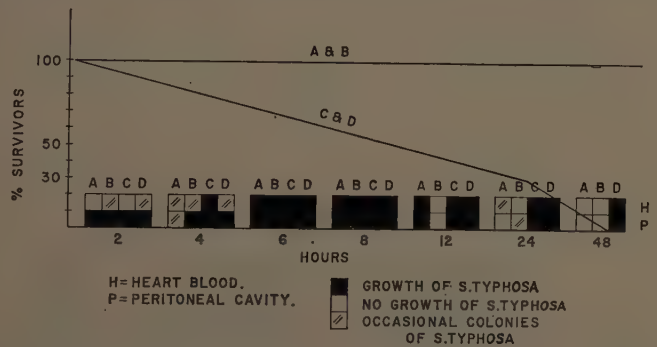


FIGURE 4. The effect of SDM in the *S. typhosa* infection of mice: A, 50 mg./kg. orally; B, 200 mg./kg. orally; C and D, controls.

with cortisone indeed antagonized the treatment with SDM. All cortisone-treated mice died, despite the active sulfonamide dose, as did the controls, and they also exhibited the same abundant growth of *S. typhosa* in the blood, whereas the sulfonamide in unconditioned mice protected 70 per cent of the animals, which were free of *Salmonella* after 12, 24, and 48 hours.

It might be mentioned that one cannot generalize these findings; preliminary experiments suggest that the effect of SDM in a staphylococcal infection was not antagonized by cortisone.

In the experiments described so far we used the routine procedure in which the infection was followed by the drug administration after 10 to 20 min. The lasting antibacterial effect of a sulfonamide just described prompted an attempt to demonstrate the activity at prolonged intervals. A few experiments were therefore carried out in which treatment with sulfonamides was instituted 8 hours after the infection with *S. typhosa* P58a or *Staphylococcus aureus* Smith at a time at which a blood infection was manifest;* the results are shown in TABLE 4.

* Special experiments were carried out to prove that, as in the *Salmonella* infection (see FIGURE 4), in staphylococcus infection, septicemia was established after 8 hours.

It is evident that the sulfonamides tested exerted also a therapeutic effect although higher doses were required. Characteristic differences as observed in the other types of experiments were also found under the conditions of delayed treatment, for example, the lower activity of SP in *S. typhosa*. The other differences were not significant, thus indicating that sulfonamides of different pharmacological type and of different degree of activity were able to

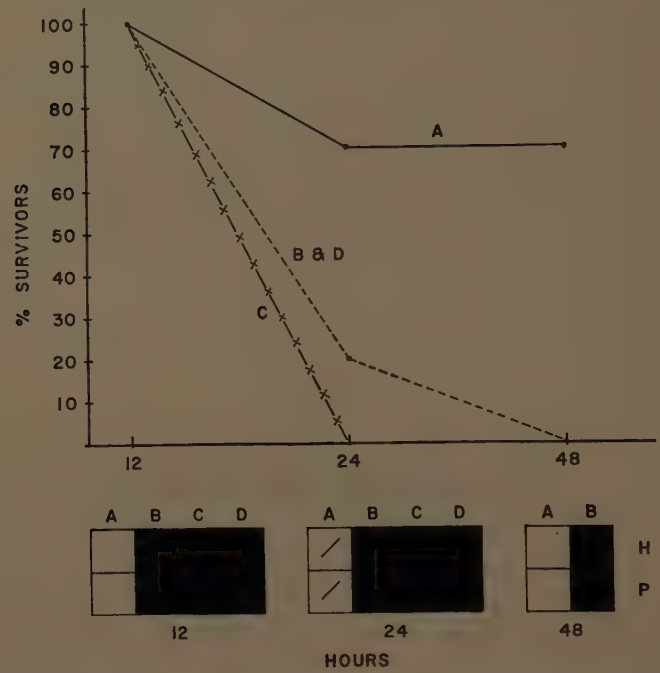


FIGURE 5. The effect of cortisone on SDM therapy for *S. typhosa* infection in mice: A, SDM (50 mg./kg.); B, SDM (50 mg./kg.) plus cortisone; D, controls (cortisone alone); C, untreated controls.

TABLE 4

THERAPEUTIC EFFECT OF 4 SULFONAMIDES IN EXPERIMENTAL INFECTIONS OF MICE WITH *S. TYPHOSA* P58a OR *STAPH. AUREUS* SMITH

S. typhosa:	infection:	1000 MLD intraperitoneally
	treatment:	166 mg./kg. 1 orally
Staph. aureus:	infection:	1000 MLD intraperitoneally
	treatment:	500 mg./kg. 3 orally

Drug	No. survivors/No. observed	
	S. typhosa	*Staph. aureus*
Sulfadimethoxine (SDM)	10/10	14/20
Sulfisoxazole (SI)	6/10	8/10
Sulfamethoxypyridazine (SMP)	8/10	8/20
Sulfaphenazole (SP)	3/10	14/20
Controls	1/10	1/20

control established septicemic infections at a stage when the primary defense of the host has been overcome by bacterial invasiveness.

Summary

A comparison of the chemotherapeutic activity of four sulfonamides against a series of pathogenic Gram-positive and Gram-negative organisms showed that long persistence in the blood was to a certain degree reflected by somewhat higher activity. The degree of activity *in vivo* was, however, independent of the toxicity.

Sulfadimethoxine was characterized by low toxicity, lasting concentration in the blood, and high activity resulting in an optimal chemotherapeutic ratio.

Sulfadimethoxine served as an example to show that pathogenic organisms (*S. typhosa*) were irreversibly damaged within a 24-hour period following the drug administration. Evidence was also produced to show that elimination of natural defense mechanisms by conditioning with cortisone antagonized the chemotherapeutic effect.

All sulfonamides tested were able to control experimental infections if treatment was delayed to a time at which septicemia had been established.

Acknowledgments

The authors gratefully acknowledge the valuable cooperation of Astrid Arnesen, Dorothy R. Kelly, and Rocco Russomanno, who carried out most of the experimental work.

References

1. Fust, B. & E. Boehni. 1959. Antibiotic Med. & Clin. Therapy. **6**(Suppl.): 3.
2. Semenitz, E. 1954. Z. Immunitaetsforsch. **111:** 388.
3. Schnitzer, R. J., W. F. DeLorenzo, E. Grunberg & R. Russomanno. 1958. Proc. Soc. Exptl. Biol. Med. **99:** 421.
4. Randall, L. O., R. E. Bagdon & R. Engelberg. 1959. Toxicol. & Appl. Pharmacol. **1:** 28.
5. Schnitzer, R. J., R. H. Foster, N. Ercoli, G. Soo-Hoo, C. N. Mangieri & M. D. Roe. 1946. J. Pharmacol. Exptl. Therap. **88:** 47.
6. Roepke, R. R., T. H. Maren & E. Mayer. 1957. Ann. N. Y. Acad. Sci. **69**(3): 457.
7. Neipp, L., W. Padowetz, W. Sackmann & J. Tripod. 1958. Schweiz. med. Wochschr. **88:** 835, 858.
8. DeLorenzo, W. F. & R. Russomanno. 1959. Antibiotic Med. & Clin. Therapy. **6** (Suppl.): 14.
9. Reed, L. J. & H. A. Muench. 1938. Am. J. Hyg. **27:** 493.
10. Domagk, G. 1957. Ann. N. Y. Acad. Sci. **69**(3): 380.
11. Schnitzer, R. J. & W. F. DeLorenzo. 1959. Antibiotic Med. & Clin. Therapy. **6** (Suppl.): 17.
12. Finland, M., W. F. Jones, Jr., Z. Mohsen & G. R. Cherrick. 1957. Am. J. Med. Sci. **234:** 505.
13. Rentchnick, P. P. 1958. Schweiz. med. Wochschr. **88:** 362.

LOW-DOSE LONG-ACTING SULFONAMIDES *ARE* DIFFERENT*

William P. Boger and John J. Gavin
Norristown State Hospital, Department of Research Therapeutics, Norristown, Pa.

There has been a regrettable and too general tendency to speak generically of "sulfonamide therapy" and to subscribe to the philosophy that all sulfa drugs are essentially the same. This dangerous and erroneous attitude is strengthened by careless statements in articles that purport to teach and guide. For example: "The sulfonamides are highly effective in the treatment of pneumococcal pneumonia. *The dosage is 6 to 8 gms. daily.*"[1] [Emphasis ours—AUTHORS.] Unfortunately, this endorsement of a common dosage schedule for the antibacterial sulfonamides has the authority of editorial comment by a panel of experts. Another example: "The successful treatment with sulfonamides depends on knowledge of the pharmacodynamic properties, since their ranges of therapeutic effectiveness are similar. Blood levels of 6 to 10 mg.% can be maintained with the oral administration of *100 mg./kg. body weight every six hours.*"[2] [Emphasis ours—AUTHORS.] This pronouncement, which implies the desirability of a knowledge of the difference between the properties of the various sulfonamides, immediately documents the "lack of such knowledge." Even casual reference to *New and Non-Official Drugs, 1959*,[3] or to the much-maligned promotional literature of the pharmaceutical houses, will confirm the error of a uniform dosage schedule of "100 mg./kg. of body weight every six hours." Taken at face value, 100 mg./kg. of body weight for a 70-kg. adult would mean 7 gm., but the dosage repeated "every six hours" would mean 28 gm./day for an average adult! These quotations may help justify the title of this paper.

Our original clinical report on sulfamethoxypyridazine[4] made it clear that this compound was rapidly absorbed from the gastrointestinal tract and very slowly excreted. Not only was a high concentration promptly *attained* in the circulation, but concentrations of a very high order were *maintained* for many hours. The half life (the time required for the concentrations of the circulating sulfonamide to decline to a value of half the peak concentration) was 24 hours in some persons and 48 hours in others. This half life of 1 to 2 days after single oral doses ranging from 0.5 to 7.5 gm. has been amply confirmed.[5-8] Similar observations of prolonged half life have been made for both sulfadimethoxine[9] and sulfaphenazole.[10]

These three new drugs—sulfamethoxypyridazine, sulfadimethoxine, and sulfaphenazole—deserve the designation low-dose long-acting antibacterial sulfonamides. Each is characterized by excellent absorption from the gastrointestinal tract, very slow urinary excretion, a low order of acetylation, acceptable solubility of both parent compound and derivatives in urine, and antibacterial activity comparable to that of sulfadiazine. The dosage schedules for sulfadimethoxine and sulfamethoxypyridazine are the same, and any differ-

* The work reported in this paper was made possible by grants-in-aid made to the Fund for Research Therapeutics, Norristown State Hospital, by Lederle Laboratories Division of American Cyanamid Company, Pearl River, N. Y., and Hoffmann-La Roche Inc., Nutley, N. J.

ences between these two compounds rest upon the further definition of the seeming differences of diffusion into the cerebrospinal fluid[4, 9, 11] and of metabolism, as suggested by differences in urinary metabolites.[12] On the other hand, sulfaphenazole must be administered in doses two times those for sulfamethoxypyridazine and sulfadimethoxine in order to attain and maintain the same order of circulating concentrations. On the basis of present information, sulfaphenazole does not diffuse through intact meninges into the cerebrospinal fluid to the same extent as the other two compounds.[10] Thus, with the qualifications regarding sulfaphenazole, these three compounds can be thought of together.

The prolonged half life of sulfamethoxypyridazine awakened our interest in the potential dangers of accumulation, when the drug is administered in excessive doses, especially to patients with unsuspected impairment of renal function. The renal clearance of sulfamethoxypyridazine is of such an extremely low order. (1 to 5 ml./min.[4, 7, 10, 13] in normal persons) that accumulation in the circulation can be anticipated in patients with compromised renal function. The defect may be so minor as to pass undetected by methods of assessing renal function other than formal renal-clearance measurements with insulin, creatinine, or para-amino hippurate (PAH).

Methods

Free and total sulfonamide estimations were made by the standard method of Bratton-Marshall,[14] using each compound as its own standard of reference. All of the values reported hereinafter relate to serum or plasma as opposed to "whole blood" concentrations of sulfonamides. In previous publications, we have expressed our opinion that there is little or no diffusion of the long-acting sulfonamides into the red blood cells, and hence it is more meaningful to compare sulfonamide medications on the basis of serum or plasma concentrations. The fact that the sulfonamide content can be accounted for almost completely in the plasma has been confirmed by others.[7, 13] Single large batches of sulfamethoxypyridazine and sulfadimethoxine were employed throughout this investigation.

Hereinafter, the term "sulfonamidemia" will be used as a synonym for serum or plasma sulfonamide concentrations.

Single small oral doses of sulfamethoxypyridazine daily. To test the hypothesis of accumulation of drug in the circulation, four patients were selected for treatment. All had complained from time to time of burning of the urine; microscopic examination had revealed both pyuria and bacilluria, but in none was urinary tract infection a prominent complaint.

In TABLE 1 are presented the free and total sulfonamidemia that resulted from administering a single oral 500-mg. dose of sulfamethoxypyridazine at 8 A.M. to 2 patients, and the results following the administration of single, oral doses of 250 mg. at 8 A.M. for periods of 5 days. In all patients, accumulation was observed. The differences between the 4- and 8-hour samplings on each day were slight, indicating the slow rate at which plasma concentrations decline. It is clear that on the fifth day the plasma concentrations were three to four times those observed on the first day. A small difference between the free and total concentrations confirms again the slight extent (10 to 24 per

cent) to which sulfamethoxypyridazine circulates as acetylated compound. These results are graphically portrayed in FIGURES 1 and 2.

Patient H.S., age 81, showed considerable accumulation of drug and an unusual increase of acetylated compound. This response was unique and has remained so to the present time. The patient's condition was poor during the period of treatment, and the nonprotein nitrogen levels fluctuated between 40 and 60 mg./100 ml. The question naturally arises as to what factor in this patient's physiology produced this seemingly increasing rate of acetylation of sulfamethoxypyridazine. Variability in the degree to which this drug is conjugated has been observed by others,[7] but no explanation has been offered. We have tested a number of sera from patients with elevated nonprotein nitro-

TABLE 1
SULFAMETHOXYPYRIDAZINE

Patient	Age	Sex	State*	Plasma concentrations, mg./100 ml.											
				1		2		3		4		5		6	
				4 hr.	8 hr.	4 hr.	8 hr.	4 hr.	8 hr.	4 hr.	8 hr.	4 hr.	8 hr.	4 hr.	8 hr.
SINGLE ORAL 500-MG. DOSE AT 8:00 A.M.															
EB	68	F	F	—†	5.1	10.1	8.8	11.4	11.6	14.0	14.1	14.2	13.0	15.8	14.0
			T	—†	5.9	11.6	10.2	13.5	13.5	16.2	16.8	16.3	15.4	18.0	16.2
RH	52	M	F	5.4	—†	8.5	14.2	9.4	8.6	10.3	9.6	11.6	10.3		
			T	6.2	—†	9.5	16.1	11.2	10.4	14.2	11.6	14.0	13.6		
SINGLE ORAL 250-MG. DOSE AT 8:00 A.M.															
HS	81	F	F	3.4	3.2	4.2	4.6	6.6	6.1	6.6	6.2	5.4	10.7		
			T	4.0	4.0	6.3	7.0	10.8	10.5	12.4	11.5	11.7	17.4		
EG	79	F	F	2.6	—†	5.7	6.0	7.3	6.2	6.9	6.6	10.1	9.6		
			T	2.9	—†	6.2	7.1	8.6	7.3	9.2	9.1	13.4	12.0		

* F indicates free drug (nonconjugated); T, total drug.
† No specimen.

gen values, and have been surprised to find that some, but not all, gave false color reactions with the Bratton-Marshall sulfonamide method (representing a concentration of from 0.5 to 1.5 mg./100 ml.).

Multiple small oral doses of sulfamethoxypyridazine daily. With the foregoing clear-cut evidence of accumulation of sulfamethoxypyridazine after single small oral doses, it was decided to extend the observations. Eight patients, evenly divided between males and females, were given 125-mg. doses 4 times during the waking day (7 and 11 A.M. and 3 and 7 P.M.) for 5 days. Blood sampling was done 1 and 4 hours after the 11 A.M. dose on each of the 5 days of observation. This pattern of sampling was regarded as appropriate to determine the maximal and minimal concentrations achieved on this schedule of dosage.

From the data of TABLE 2 it is again clear that accumulation occurs in all

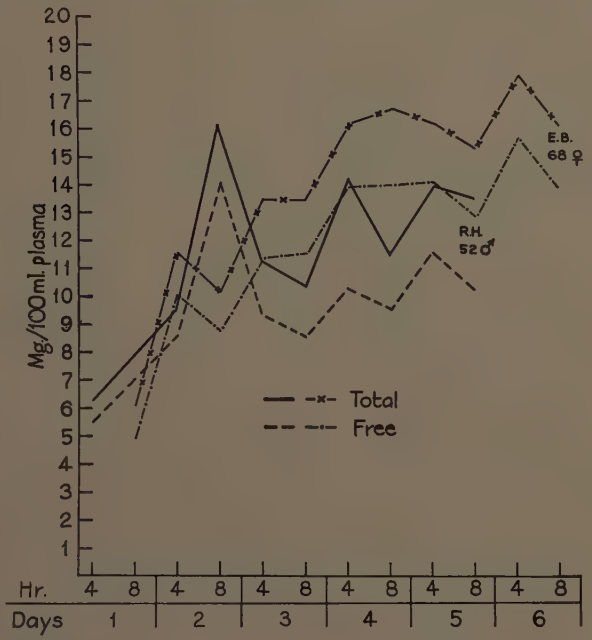


FIGURE 1. Sulfamethoxypyridazine, 500 mg. oral dose daily.

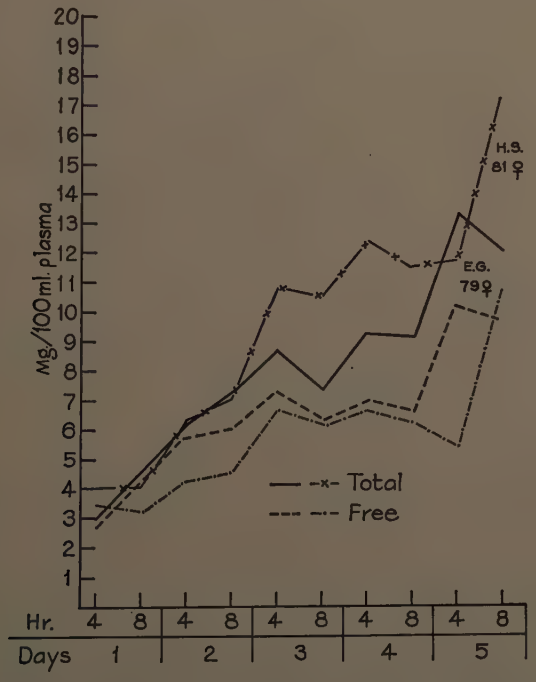


FIGURE 2. Sulfamethoxypyridazine, 250 mg. oral dose daily.

patients and that a "plateau" was achieved only in patients O.K. and L.D., the concentrations on the fourth day of treatment of these patients being essentially the same as those observed on the fifth day of treatment. The slight decline between doses is again observed, and the minor degree to which the drug is acetylated is reaffirmed. Variability between patients is observed, and the difference between patient L.F., age 36, and patient E.W., age 87, is particularly striking. On the same schedule of treatment the younger of these

TABLE 2
SERUM CONCENTRATIONS OF SULFAMETHOXYPYRIDAZINE (KYNEX) AFTER ORAL MULTIPLE-DOSE THERAPY*

Patient	Age	Sex	Weight	State†	Day 1		Day 2		Day 3		Day 4		Day 5	
					1 hr.	4 hr.	1 hr.	4 hr.	1 hr.	4 hr.	1 hr.	4 hr.	1 hr.	4 hr.
EW	87	F	97	F	4.6	4.3	11.8	11.1	14.8	16.4	18.4	18.4	21.0	20.6
				T	5.6	4.5	12.4	12.8	17.0	18.8	20.6	20.6	24.0	23.2
DH	83	F	91	F	3.8	3.3	9.5	8.5	13.8	13.1	13.7	12.9	16.4	15.4
				T	4.0	4.0	10.8	10.2	16.2	15.7	16.1	15.5	18.8	18.5
MB	74	F	133	F	4.6	3.4	8.3	7.7	11.7	10.2	12.7	11.3	13.7	13.3
				T	5.5	3.9	9.7	8.9	13.7	10.8	14.9	13.5	15.7	15.5
AH	83	F	73	F	5.5	3.8	6.1	5.9	12.1	10.6	12.6	12.1	14.4	14.1
				T	6.1	5.5	7.7	7.7	14.7	13.7	16.0	15.7	18.0	18.0
Female average				F	4.6	3.7	8.9	8.3	13.1	12.6	14.4	13.7	16.4	15.8
				T	5.3	4.5	10.1	9.9	15.4	14.7	16.9	16.3	19.1	18.8
OK	55	M	203	F	1.4	2.5	6.5	5.5	6.6	7.8	10.0	9.5	9.5	9.6
				T	1.8	3.1	7.7	6.6	7.9	9.0	11.3	11.2	11.2	11.3
LF	36	M	130	F	0.4	0.5	3.7	3.2	3.9	5.0	5.3	4.8	7.6	6.7
				T	0.6	0.8	4.4	4.0	4.8	6.0	6.6	6.1	9.0	8.2
JF	47	M	161	F	1.9	3.1	7.5	6.7	7.1	7.5	10.6	9.8	11.1	11.1
				T	2.2	3.7	8.5	7.8	8.3	9.0	12.3	11.8	13.3	13.1
LD	68	M	138	F	1.5	3.0	5.3	5.5	6.2	6.6	10.4	9.5	9.4	7.9
				T	2.2	3.9	7.3	7.4	9.5	9.1	13.5	12.6	12.6	10.9
Male average				F	1.3	2.3	5.7	5.2	5.9	6.7	9.1	8.4	9.4	8.8
				T	1.7	2.9	6.9	6.4	74	8.3	10.9	10.4	11.5	10.9
Male and female average				F	2.9	3.0	7.3	6.8	9.5	9.7	11.8	11.0	12.9	12.3
				T	3.5	3.7	8.5	8.2	11.4	11.5	13.9	13.4	15.3	14.9

* Dosage: 125 mg. q.i.d. for 5 days.
† F indicates free drug (nonconjugated); T, total drug.

patients attained a concentration of only 7.6 mg./100 ml. of free compound, whereas the older patient attained a level of free drug almost 3 times as great —21 mg./100 ml.

These observations are portrayed more graphically in FIGURES 3, 4, and 5.

Multiple small oral doses of sulfadimethoxine. As noted above, sulfamethoxypyridazine and sulfadimethoxine have acted quite similarly with regard to the peak plasma concentrations attained and the high orders of sulfonamidemia that are maintained. An additional group of 8 patients, evenly divided between males and females, was given 125 mg. of sulfadimethoxine 4 times daily

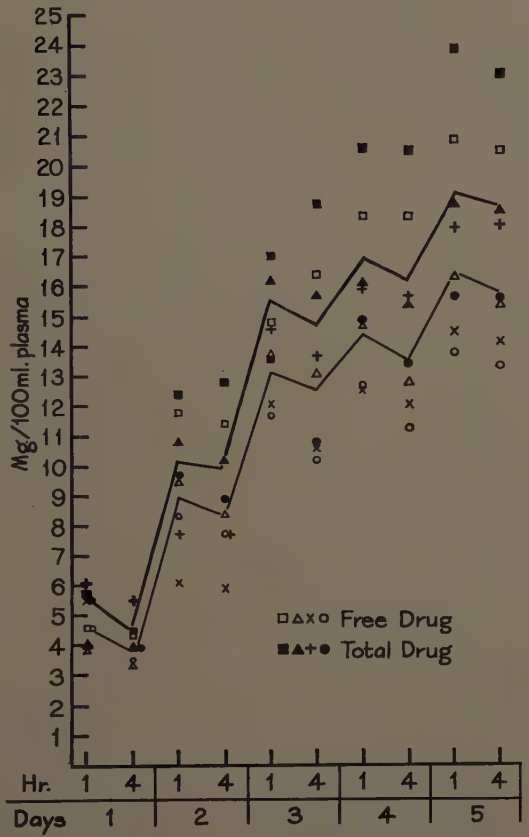


FIGURE 3. Sulfamethoxypyridazine, 125 mg. orally 4 times daily; 4 female patients.

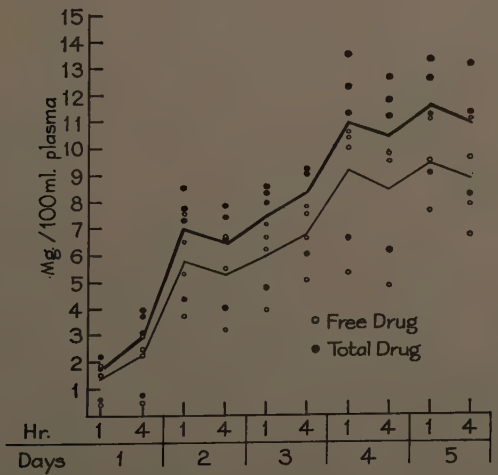


FIGURE 4. Sulfamethoxypyridazine, 125 mg. orally 4 times daily; 4 male patients.

(7 and 11 A.M. and 3 and 7 P.M.) for 5 consecutive days. The results are shown in detail in TABLE 3. Accumulation of drug occurred in all patients *except* T.D., age 49. When our study was almost completed, this patient presented us with a handful of the capsules that he was supposed to have ingested. There had been no failure in presenting the patient with the drug to be taken at the prescribed times, and close questioning of the nurses assured us that the patient

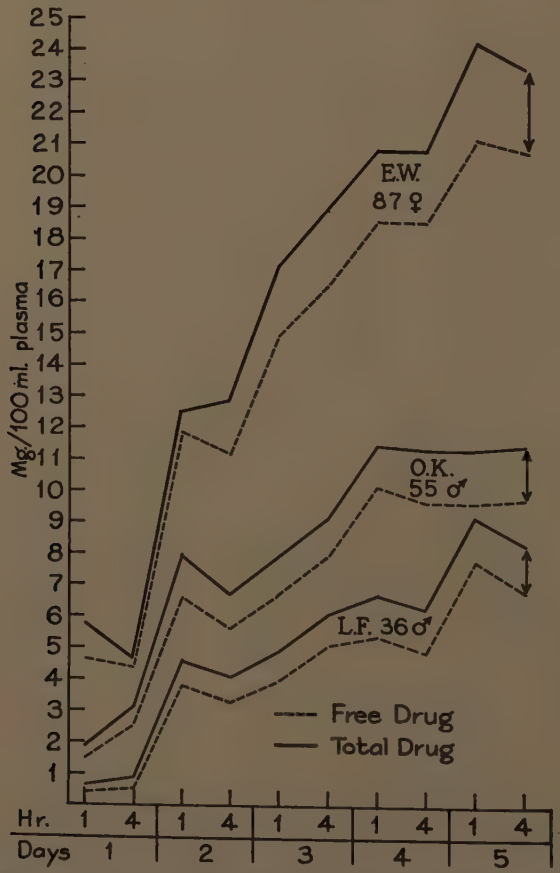


FIGURE 5. Sulfamethoxypyridazine, 125 mg. orally 4 times daily.

had swallowed the medication. This discovery explains much more simply the deviation of this patient from the pattern of the group than would the invocation of some subtle metabolic difference in the handling of the medication. We humbly suggest that many irregularities in clinical data are more readily accounted for by some such happening as that just cited than by some physiological or pharmacological subtlety.

Again, a low order of acetylation and an increase by 3 to 4 times of the plasma concentration during the 5-day period of treatment are observed. These data are presented graphically in FIGURES 6 and 7.

Discussion

The accumulation of long-acting sulfonamides in the circulation was anticipated and several investigators have clearly shown the prolonged half life (24 to 48 hours) of sulfamethoxypyridazine and sulfadimethoxine. Accumulation has been observed with sulfamethoxypyridazine after a variety of dosage schedules: (1) initial doses of 2 gm., followed by 1 gm. every 4 hours;[5] (2) 1 gm. initially, followed by 0.5 gm. every 24 hours;[5] (3) 0.5 gm. every 12 hours;[13]

TABLE 3
SERUM CONCENTRATIONS OF SULFADIMETHOXINE (MADRIQID) AFTER ORAL MULTIPLE-DOSE THERAPY*

Patient	Age	Sex	Weight	State†	Day 1		Day 2		Day 3		Day 4		Day 5	
					1 hr.	4 hr.	1 hr.	4 hr.	1 hr.	4 hr.	1 hr.	4 hr.	1 hr.	4 hr.
JMcC	49	M	128	F	2.5	5.1	8.7	9.2	15.5	12.7	14.4	14.6	16.1	16.4
				T	2.6	5.4	9.1	9.8	17.5	14.2	16.5	16.5	18.3	18.7
TD	49	M	196	T	0.1	1.8	2.4	3.9	3.6	3.5	2.1	2.0	2.7	2.5
				T	0.1	2.0	2.9	4.3	4.3	4.1	2.6	2.8	3.2	2.9
WMcC	54	M	161	F	1.2	2.3	6.6	6.1	7.7	9.3	8.3	10.0	11.5	11.8
				T	1.5	2.5	6.8	6.8	8.6	10.6	9.4	11.4	13.1	13.4
TA	71	M	157	F	0.8	2.0	5.7	6.6	7.6	9.0	12.5	12.5	11.7	13.2
				T	0.9	2.2	6.5	7.4	8.7	10.5	14.4	14.9	13.8	15.6
Male average				F	1.5	3.1	7.0	7.3	10.3	10.3	11.7	12.4	13.1	13.8
				T	1.7	3.4	7.5	8.0	11.6	11.8	13.4	14.3	15.1	15.9
EW	79	F	104	F	4.0	5.4	9.8	11.5	16.3	14.5	17.3	17.2	17.4	18.8
				T	4.7	7.9	11.3	13.4	19.1	16.8	20.7	20.9	20.9	22.6
LN	89	F	101	F	3.1	4.1	8.9	9.2	14.5	14.0	17.6	15.9	18.6	16.5
				T	3.7	5.0	10.2	11.0	16.8	16.3	20.6	19.0	21.9	19.7
MV	84	F	107	F	3.2	3.8	8.5	9.0	12.9	12.1	15.5	15.9	17.3	16.9
				T	3.4	4.1	9.1	9.7	14.2	13.4	17.3	17.5	19.2	19.1
MS	87	F	86	F	3.4	4.5	10.5	11.6	15.4	15.1	15.7	15.7	17.6	16.7
				T	3.9	5.2	11.7	13.2	17.6	17.8	18.6	18.7	20.6	19.7
Female average				F	3.4	4.4	9.4	10.4	14.8	13.9	16.5	16.2	17.7	17.2
				T	4.4	5.5	10.6	11.8	16.9	16.1	19.3	19.0	20.6	20.3
Male and female average				F	2.5	3.8	8.2	8.9	12.6	12.1	14.1	14.3	15.4	15.5
				T	3.1	4.5	9.1	9.9	14.3	13.9	16.4	16.8	17.8	18.1

* Dosage: 125 mg. q.i.d. for 5 days.
† F indicates free drug (nonconjugated); T, total drug.

and (4) 50 mg./kg. once daily to children.[8] Similar accumulation has been observed in children given daily doses of 25 mg./kg. of both sulfamethoxypyridazine and sulfadimethoxine.[8, 15] Even when 1 gm. was administered every 48 hours, increasing peak values were observed during a period of 12 days.[16] The foregoing evidences of accumulation were all found after oral administration of the long-acting sulfonamides. An even more critical set of observations was made in children after the intravenous administration of an initial dose of 40 or 50 mg./kg. and, thereafter, 20 to 25 mg./kg. every 12 hours.[17]

The foregoing data attest to the phenomenon of accumulation of the low-

dose, long-acting antibacterial sulfonamides. Steadily increasing plasma concentrations have been observed after oral and parenteral administration of the drug, when single 1-gm. oral doses have been given as infrequently as every 48 hours, and our data show that, with no initial loading dose, daily doses of as little as 0.5 gm. and, in a few patients, as little as 250 mg. per day, give rise to accumulation.

Review of all of the above-mentioned references reveals 2 outstanding particulars. Despite the high order of both the attained and maintained concentra-

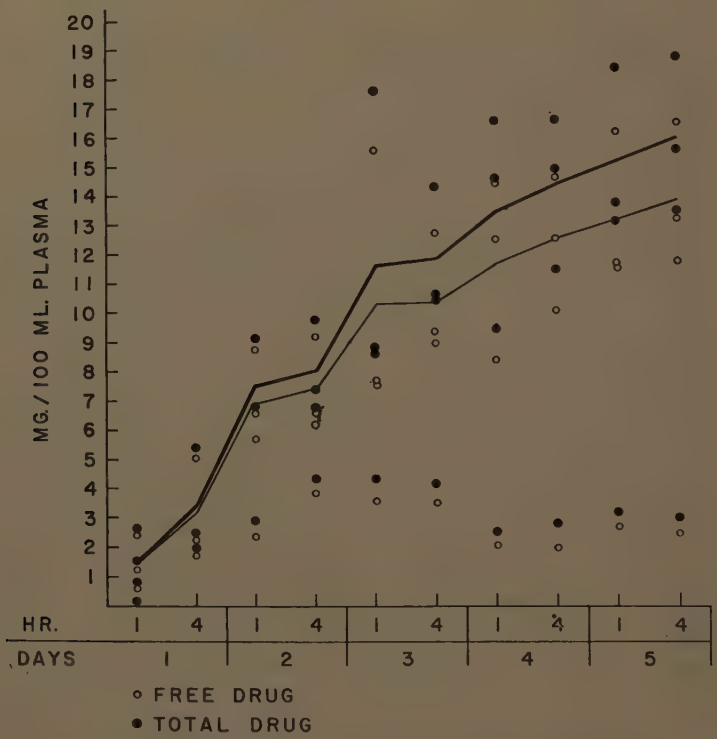


FIGURE 6. Sulfadimethoxine (Madriqid), 125 mg. orally 4 times daily; 4 male patients.

tions of sulfonamide, when the low-dose, long-acting sulfamethoxypyridazine and sulfadimethoxine have been administered, the number of side effects has been remarkably few. Secondly, regardless of whether serum or plasma or whole blood determinations of sulfonamide concentrations have been made, the lowest levels observed immediately before administration of the next dose have been of a very high order, and have averaged 10 mg./100 ml. or higher; both these facts merit comment.

The most frequently observed side effects have been headache, nausea and vomiting, drowsiness and malaise, dizziness, rash and, in a few cases, psychosis. With the exception of rash, one is prompted to regard all of these symptoms as evidences of mild central nervous system disturbance. One of us (W.P.B.)

has pointed out[4, 18] that sulfamethoxypyridazine diffuses in larger total amount into the cerebrospinal fluid than do any of the other sulfonamides studied. It is perhaps too ready an explanation, but it is of interest to observe that, whereas the sulfonamidemias are comparable, the record fails to show the same amount of headache, nausea and vomiting, and lassitude with sulfadimethoxine, and this drug diffuses to a lesser degree into the cerebrospinal fluid.[9] Mild psy-

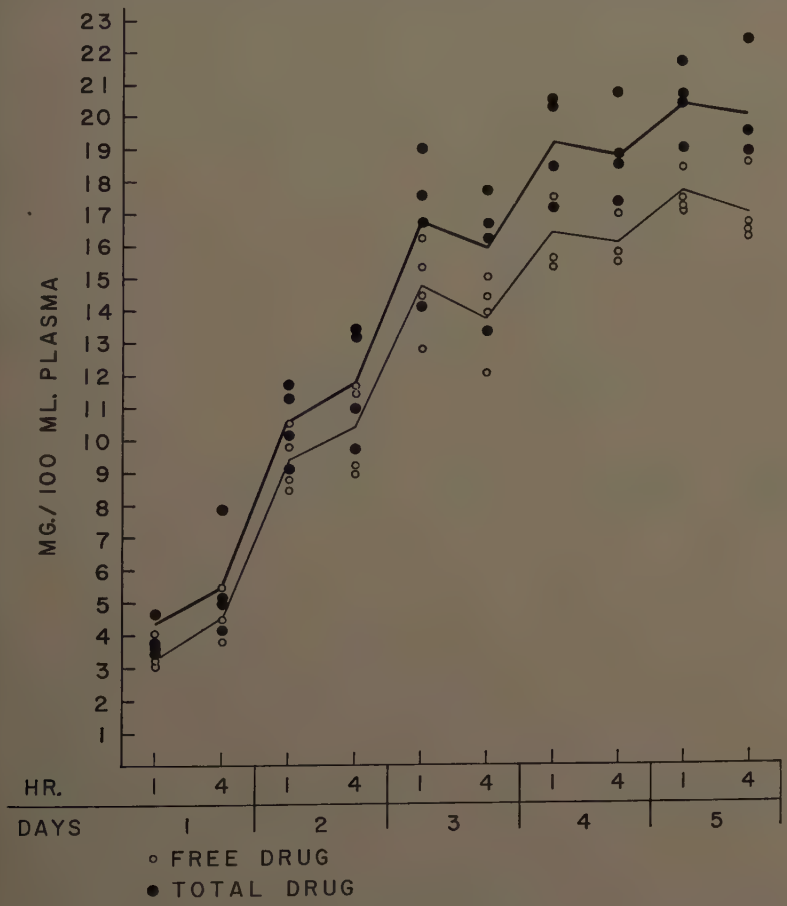


FIGURE 7. Sulfadimethoxine (Madriqid), 125 mg. orally 4 times daily; 4 female patients.

chosis is not new, for the older literature calls attention to psychosis occurring in pneumonia patients treated with sulfadiazine.[19, 20] Similar observations of psychotic behavior appearing in pneumonia patients treated in India with sulfamethoxypyridazine[21, 22] have been made.

Rather than explain the side effects that have been observed with the new low-dose, long-acting sulfonamides simply as "toxicity" of these drugs, we are inclined to assign the cause to "excessively high circulating concentrations." The tendency to accumulation, on the basis of an extremely low renal clearance rate, has been noted above. One of us (W.P.B.), while working with two other

compounds (carinamide and probenecid) belonging chemically to the group of sulfonamide drugs, has observed nausea and vomiting, lassitude, drowsiness, and headache following intravenous infusion when plasma concentrations exceeded 30 mg./100 ml. These observations strengthen our opinion that most of the side effects presently being reported are due either to the administration of mistakenly high doses or to proper doses to patients with unsuspected impairment of renal function, with resulting excessively high circulating concentrations of sulfamethoxypyridazine and sulfadimethoxine. The pharmacology of both of these agents supports these likelihoods. In this connection, it is of interest that lassitude and headache were observed 4 to 8 hours after a single 3-gm. dose of sulfamethoxypyridazine in half the patients.[16]

For several years sulfonamides have been "standardized" in terms of their ability to *attain* and *maintain* a therapeutic concentration of 10 to 15 mg./100 ml. of whole blood (20 to 30 mg./100 ml. of plasma). Concentrations of this order of magnitude can certainly be achieved with most of the presently available antibacterial sulfonamides that are used for the treatment of systemic disease, but the extent to which such concentrations are maintained is a matter of considerable question. Certainly, the new low-dose long-acting antibacterial sulfonamides, sulfamethoxypyridazine and sulfadimethoxine, are absorbed as rapidly as any available sulfonamide drug and attain peak concentrations of the same magnitude as those attained by using doses that are 2 or 3 times as large. Even the "loading doses" of 4 and 6 gm. of the commonly employed systemic antibacterial sulfonamides (sulfisoxazole, tri-sulfapyrimidines, sulfasomidine, sulfaethidole) do no more than equal the peak concentrations observed with 1 or 2 gm. of the low-dose, long-acting sulfonamides, and the half lives of these common sulfonamides are much shorter. It would seem appropriate to inquire whether the older and more familiar sulfonamide drugs do, in fact, *maintain* therapeutic concentrations in the same degree as is average performance for the long-acting sulfonamides.

The low-dose, long-acting sulfonamide drugs have been evaluated extensively in normal individuals and in patients suffering from diseases in which dehydration, high fever, and disturbed physiology have not been prominent. Yet, they have uniformly maintained circulating concentrations of a high order. For example, on a schedule of 1 gm. of sulfamethoxypyridazine every 12 hours, concentrations were "maintained at a fixed level of about 17 mg./100 ml. of whole blood."[23] Of 125 random specimens obtained from patients receiving 0.5 gm. of sulfamethoxypyridazine daily, the mean concentration was 10.3 mg./100 ml. of serum.[7] In a group of children, it was found that 30 mg./kg. once weekly gave mean concentrations throughout the week of a higher level than those obtained following the daily administration of 1 gm. of sulfadiazine.[24] All available data show that the new low-dose, long-acting antibacterial sulfonamides not only *attain* but *maintain* sulfonamidemia of a high order with a minimum of inconvenience to patients and physician. The high circulating concentrations that have been observed in normal persons (volunteers) can be anticipated to be much higher in elderly, dehydrated, and febrile patients. The pharmacology of these new drugs must be thoroughly understood so that side effects may be interpreted in many cases as due to inadvertent overdosage rather than primary toxicity.

The above data show clearly that accumulation of drug in the circulation can occur following daily doses as small as 0.5 gm. in all patients, and that in some persons of advanced age a dose as small as 0.25 gm. may cause such accumulation. However, if sulfonamide treatment is begun with doses as small as this, a period, longer than desirable, elapses before optimal therapeutic concentrations are achieved. Accordingly, the use of a priming or loading dose at the outset of treatment is mandatory. One, or at most, 2 gm. of either sulfamethoxypyridazine or sulfadimethoxine is sufficient for such an initial dose. Thereafter, 0.5 gm./day administered either as a single or divided dose would be sufficient for the majority of patients and, in some persons of advanced age or with compromised renal function, it would be an excess. In exceptional situations, the decision may be made to administer as much as 1 gm. per day for 3 to 5 days, but it must be accepted that accumulation will occur on such a dosage schedule, and concentrations in the blood may be reached that will produce side effects and toxicity.

The low-dose, long-acting sulfonamides are able to maintain circulating concentrations of drugs more constantly than is possible with any schedule of dosage employing the more conventional sulfonamides. The level at which these concentrations are established is not only a function of the dosage schedule, but also of the patient's basic physiology and his illness. Individualization of treatment is the ideal of therapy, and this is possible to a nicety with the new, long-acting sulfonamides; however, in order to make the best adaptation of the treatment to the patient's need, the dosage schedule should be adjusted and controlled with the aid of serum or blood determinations of sulfonamide content.

Conclusions

Data have been presented to show that sulfamethoxypyridazine and sulfadimethoxine, when administered 4 times daily in a dose of 125 mg., produce increasing plasma concentrations during a 5-day period of treatment. During this 5-day period, plasma concentrations increase from 2 to 4 times. These observations clearly show an accumulation phenomenon on the basis of the extremely slow renal clearance of these drugs. There is some suggestion that aging compromises renal function in such manner as to be reflected by accumulation of long-acting sulfonamides in the circulation to a greater degree than is observed in persons with normal and "younger" kidneys.

The new low-dose, long-acting sulfonamides probably attain and maintain therapeutic concentrations of a higher order than is common with the use of conventional doses of the majority of currently available systemic sulfonamide drugs. In order that these new agents be used to greatest advantage, it is imperative that the low daily dosage requirement be clearly distinguished from that of the conventional sulfonamides and that, before side effects are assigned to toxicity of the drug, it be ascertained whether excessive doses have been administered or whether unsuspected renal impairment has contributed to the accumulation of excessively high concentrations of the sulfonamide. These drugs have antibacterial actions comparable to those of any of the other sulfonamides and make possible great flexibility of dosage schedules applicable to

the treatment of usual infections, but uniquely applicable to programs of prophylaxis.

Acknowledgment

We are indebted to Myron M. Shoemaker for his technical assistance.

References

1. Report of Committee on Chemotherapy and Antibiotics. 1958. Am. Coll. Chest Phys. Chemotherapy of specific infectious diseases of the lower respiratory tract. J. Diseases of the Chest. **33:** 435–440.
2. Straffon, R. A. 1958. Treatment of infections with single antibiotics or chemotherapeutic agents. Univ. Mich. Med. Bull. **24:** 153–158.
3. New and Non-Official Drugs. 1959. : 47–63. Lippincott. Philadelphia, Pa.
4. Boger, W. P., S. C. Strickland & J. Gylfe. 1957. Sulfamethoxypyridazine (Kynex), a new long-acting sulfonamide. Antibiotic Med. & Clin. Therapy. **3:** 378–387.
5. Finland, M., W. F. Jones, Jr., M. Ziai & G. R. Cherrick. 1957. Sulfamethoxypyridazine: concentrations in blood and urine during oral administration of various dosages. Am. J. Med. Sci. **234:** 505–516.
6. Foerster, D. K., W. J. Martin, W. F. McGuckin & D. R. Nichols. 1956. Concentrations in blood of sulfaethylthiadiazole, sulfamethoxypyridazine and sulfadiazine after oral administration. Proc. Staff Meetings Mayo Clinic. **31:** 678–683.
7. Jackson, G. G. & H. G. Grieble. 1957. Sulfamethoxypyridazine: pharmacological observations and clinical use in the treatment of urinary tract infections. Ann. N. Y. Acad. Sci. **69**(3): 493–500.
8. Ross, S., W. E. Ahrens & E. A. Zaremba. 1957. Sulfamethoxypyridazine, a long-acting sulfonamide: some preliminary clinical and laboratory observations in infants and children. Ann. N. Y. Acad. Sci. **69**(3): 501–508.
9. Boger, W. P. 1959. A new long-acting antibacterial sulfonamide, 2,4-dimethoxy-6-sulfanilamido-1,3-diazine: a comparative study. Antibiotics Ann. 1958–1959. : 48–55.
10. Boger, W. P. 1959. Sulfaphenazol, "Orisul," a long-acting antibacterial sulfonamide. J. Am. Geriat. Soc. **7:** 314.
11. Boger, W. P. 1959. Sulfonamides old and new: a perspective. Privately published.
12. Koechlin, B. A., W. Kern & R. Engelberg. 1959. A comparative study of the metabolism and the urinary excretion of 2,4-dimethoxy-6-sulfanilamido-1,3-diazine (Madribon). Antibiotic Med. & Clin. Therapy. **6:** 22–31.
13. Jones, W. F. & M. Finland. 1957. Sulfamethoxypyridazine and sulfachloropyridazine. Ann. N. Y. Acad. Sci. **69**(3): 473–484.
14. Bratton, A. C. & E. K. Marshall, Jr. 1939. A new coupling component for sulfanilamide determination. J. Biol. Chem. **128:** 537.
15. Ross, S., J. R. Puig & E. A. Zaremba. 1959. Sulfadimethoxine, a new long-acting sulfonamide. Antibiotics Ann. 1958–1959. : 56–63.
16. Nichols, R. L. & M. Finland. 1957. Absorption and excretion of sulfamethoxypyridazine: a new long-acting sulfonamide. J. Lab. Clin. Med. **49:** 410–421.
17. Smith, G. F., R. W. Heffner, W. W. Cleveland & R. B. Lawson. 1959. Blood and cerebrospinal fluid levels of sulfamethoxypyridazine after intravenous administration in children. Antibiotics Ann. 1958–1959. : 69–74.
18. Boger, W. P. 1959. The diffusion of sulfonamides into the cerebrospinal fluid: a comparative study. Antibiotic Med. & Clin. Therapy. **6:** 32–40.
19. Stuart, M. M. & M. F. Colleen. 1944. Psychosis associated with sulfadiazine therapy. Permanente Foundation (Oakland, Calif.) Med. Bull. **2:** 153.
20. Lehr, D. 1957. Clinical toxicity of sulfonamides. Ann. N. Y. Acad. Sci. **69**(3): 417–447.
21. Kamath, P. G., U. K. Sheth, M. J. Shah & B. S. Kulfarni. 1958. Clinical evaluation and toxicity of sulfamethoxypyridazine. Indian J. Med. Sci. **12:** 892–897.
22. Parekh, J. G. & M. L. Adiga. 1958. Toxic psychosis associated with sulfamethoxypyridazine (Lederkyn). Indian J. Med. Sci. **12:** 898–907.
23. Frisk, A. R. & A. Wassen. 1958. Clinical evaluation of sulfamethoxypyridazine. Antibiotics Ann. 1957–1958. : 424–427.
24. Lepper, M. H., A. J. Simon & C. J. Marienfeld. 1957. Use of sulfamethoxypyridazine in the prevention of streptococcal infections in rheumatic patients. Ann. N. Y. Acad. Sci. **69**(3): 485–492.

COMPARATIVE SENSITIVITY OF PATHOGENIC BACTERIA TO MODERN ANTIBACTERIAL AGENTS

B. H. Leming, Jr. and Clyde Flanigan, Jr.

Division of Pathology and Microbiology, University of Tennessee and City of Memphis Hospitals, Memphis, Tenn.

In order to meet the problem of increasing organismal resistance to antibacterial agents, it is necessary to maintain constant surveillance of changing sensitivity patterns. Reports of these fluctuations should be made available continuously to any individual concerned with antibacterial therapy. Such data, because they deal with immediate conditions, should be published as soon after assimilation as possible, because the time lapse between the gathering of the data and publication may well render it inapplicable at the time of issue. Because of the regional limitations frequently characteristic of such data, individuals in local medical societies should assume responsibility for their dissemination. All practicing physicians should be reached through either local bulletins and journals or through reports at periodic group meetings.

Because a great many variables affect the sensitivity of pathogenic organisms to antimicrobial agents, it is possible to determine the relative efficacy of different agents only if they are compared in the same controlled study for a period sufficiently long to take temporary variations into consideration. The responsibility for compilation of such material lies with either the clinical pathologist, the clinical bacteriologist, or any clinician who is constantly active in the bacteriology laboratory.

Detailed sensitivity studies are presented below on approximately 7000 Gram-positive cocci isolated from specimens submitted to the clinical bacteriology laboratory of the University of Tennessee and City of Memphis Hospitals for a 21-month period. Graphic illustrations of monthly and seasonal variations in sensitivity patterns are presented, showing that the practicing physician should constantly utilize bacterial culture and sensitivity as a guide for effective antimicrobial therapy. This is especially true in relation to the currently troublesome staphylococcal infections. Culture and sensitivity studies followed by adequate antibacterial therapy and necessary adjunctive measures in the treatment of staphylococcal infections undoubtedly aid in slowing the development of organismal resistance. In most instances such procedures also will rapidly remove a potential source of infection from an environment. The practice of using surgical incision and drainage as the only treatment of lesions such as staphylococcal soft-tissue infections is illogical and unwise. In many instances, such a practice keeps a constant source of potential infection within an environment for days, weeks, and even months.

Consideration is also given below to the much discussed question of tube-dilution sensitivity studies versus the sensitivity disk method. There is no doubt as to the value of tube dilution in certain situations. However, honest consideration must be given to conditions under which the average hospital bacteriological service functions.

The problem of *in vitro* sulfonamide sensitivity tests is discussed in the light of various influencing factors—for example, the blood and the para-amino-

benzoic acid (PABA) content of the medium. Regardless of the advantages afforded by specifically designed liquid or agar media, many observers are ready and able to condemn them. It has been our experience that sulfonamide sensitivity percentages are disastrously low, regardless of the medium used,[1] and it is our contention that an adequate procedure for performing these tests should be found and adopted. Otherwise, the physician should use sulfas on clinical impression alone, to avoid the possibility of being misled by an erroneous *in vitro* test result.

Correlation and Interpretation of Sensitivity Patterns of Antimicrobial Agents

Method of study. From April, 1957, through December, 1958, patterns of susceptibility to various antimicrobial agents were established for more than 7000 cultures (yielding Gram-positive cocci) received by the clinical bacteriology laboratory of the University of Tennessee and City of Memphis Hospitals. The antimicrobial agents tested were broad- and medium-spectrum antibiotics, restricted-use antibiotics, and chemotherapeutic agents. The original series of 5600 organisms has been reported.[1] Specimens from patients were routinely cultured as follows.

(1) Blood specimens were inoculated into thioglycollate medium (BBL*) and a combination of trypticase soy-agar slant and trypticase soy-broth bottle (Castenada technique).

(2) Stool specimens were inoculated onto bismuth sulfite agar (Difco†), MacConkey agar (Difco), S.S. agar (Difco), and into selenite broth (BBL). If a *Micrococcus* was suspected, a blood plate was also inoculated.

(3) Other specimens, such as sputum, urine, and exudates, were inoculated onto blood-enriched trypticase agar (BBL), MacConkey agar, and thioglycollate broth.

In the original series,[1] the sensitivity studies were done on blood agar. Since the reporting of that series, we have selected for use trypticase agar with added 5 per cent human blood-bank blood. We are now routinely testing each organism with high-concentration sensitivity disks (BBL). For correlation, we periodically run tube-dilution sensitivity tests with all routinely used antibacterial agents.

The organisms described in *Sulfonamide Sensitivity Studies* below were selected for the sensitivity disk tube–dilution comparative study. Fifty pathogens isolated from clinical material were selected, and these included strains of *Salmonella*, *Shigella*, coagulase-positive and coagulase-negative staphylococci, *Proteus*, *Pseudomonas*, *Escherichia coli* (strain .026), and streptococci. In the comparative study described above, constant technique was practiced, as it was in the sensitivity studies that follow. This included the use of a 4- to 6-hour broth culture, a constant amount of inoculum, and an 18-hour period of incubation before interpretation. More complete details of the study method are given below.

Discussion. TABLE 1 contains susceptibility data on approximately 7000 Gram-positive cocci. Included are approximately 2300 strains of coagulase-

* Baltimore Biological Laboratory, Inc., Baltimore, Md.
† Difco Laboratories, Inc., Detroit, Mich.

positive staphylococci, 2400 strains of coagulase-negative staphylococci, and 1200 strains of beta hemolytic streptococci. The indicated susceptibility to 9 selected antibiotics is presented because the group constitutes the majority of antibiotics used in our institution. However, it represents only a segment of our routine sensitivity studies. Significant data on kanamycin, ristocetin, and vancomycin will soon be available. At present we are preparing to test pathogens supplied by a number of hospitals in an area of several hundred square miles. The preliminary indications are that we shall see not only already proved regional differences in susceptibility, but also local (county to county) differences and even significant variations between institutions within the same city. Until we are sure of the extent of the area to which our results may apply,

TABLE 1

SUSCEPTIBILITY PATTERNS OF 7000 GRAM-POSITIVE ORGANISMS EXPRESSED AS PERCENTAGES OF THE TOTAL SERIES AND OF EACH STRAIN SUSCEPTIBLE TO THE ANTIBIOTIC

		Total Gram-positive series	*Staph. aureus* coagulase positive	*Staph. aureus* coagulase negative	Beta *Streptococcus*	*Diplococcus pneumoniae*	*Str. viridans*	Anaerobic *Streptococcus*	*Micrococcus* Species	Gamma *Streptococcus*	*Str. fecalis*	Microaerophilic *Streptococcus*	*Staph. albus*	Alpha *Streptococcus*
Tetracycline.....	30 μg.	62	43	59	95	87	89	91	100	91	51	88	67	100
Oxytetracycline...	30 μg.	57	39	49	95	97	89	93	75	91	46	86	67	100
Chlortetracycline..	30 μg.	62	41	60	97	98	94	97	100	91	69	89	67	100
Chloramphenicol..	30 μg.	75	56	71	97	95	93	96	100	96	70	84	100	100
Erythromycin.....	15 μg.	76	57	79	89	98	94	93	86	89	82	86	100	100
Oleandomycin.....	15 μg.	89	92	90	96	99	96	83	100	92	71	71	100	100
Novobiocin.....	100 μg.	95	94	93	96	93	96	86	100	—	86	86	—	—
Penicillin.....	10 u.	52	27	54	91	97	87	84	75	79	55	70	33	50
Streptomycin.....	100 μg.	41	38	57	17	13	36	50	50	71	21	51	67	100

we suggest that our studies serve only as a rough guide. It is not our desire that they influence any community in which they are not applicable. As stated above, we strongly encourage other investigators to use similar restrictions, especially when dealing with antibiotics used sufficiently long to have shown definite patterns of changing susceptibility.

The demonstration of monthly and seasonal variation shown in FIGURE 1 compels us to discourage any clinician from using either past experience or clinical judgment as sole criteria for his choice of an antibacterial agent. The "blind use" (without culture and sensitivity) of antimicrobials can be likened to the game of Russian roulette. FIGURE 1 shows that, from one month to the next, susceptibility may change either positively or negatively as much as 35 per cent. FIGURE 2 is presented to further discredit nonlaboratory criteria for antimicrobial choice. The hospital and clinical isolates have been divided into respective categories and plotted against their combined pattern for com-

parison. Isolates from clinic patients would be comparable to those seen in the physician's office. It can be seen that within the same institution in a given month there may be significant differences in the susceptibility of clinic pathogens and hospital pathogens. Therefore, in the face of such variation, the clinician cannot arbitrarily use the same criteria in both office and hospital for effective antimicrobial therapy.

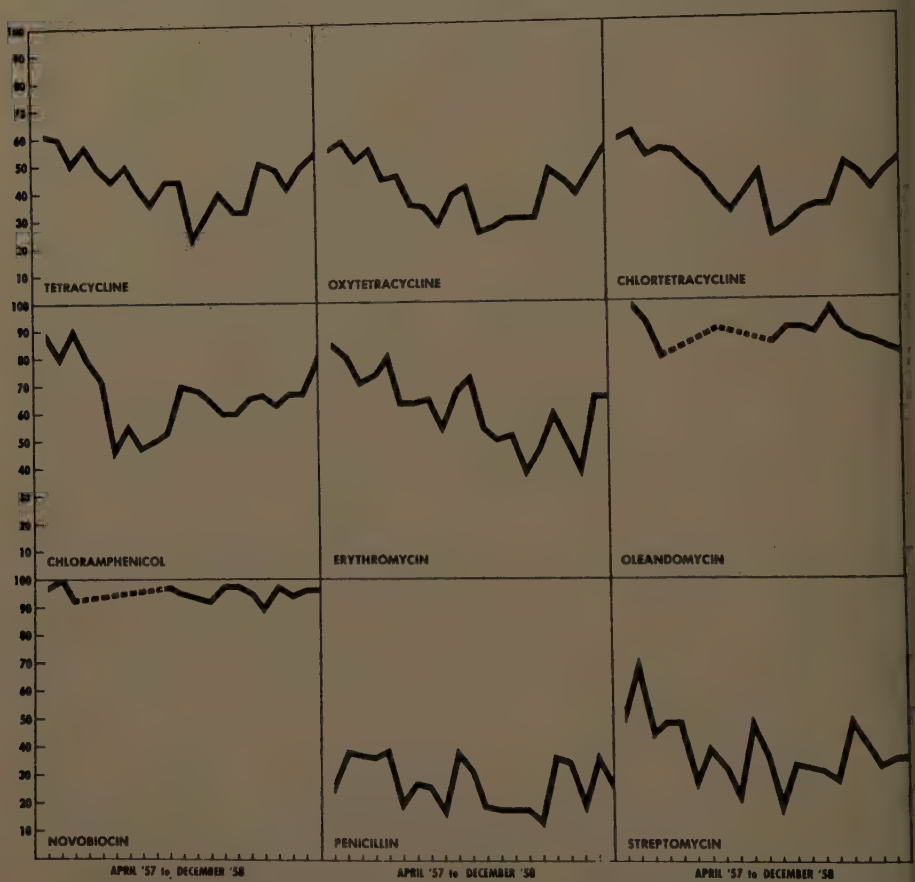


FIGURE 1. Changing susceptibility of approximately 2300 (TABLE 1) coagulase-positive staphylococci during a 21-month period. Susceptibility is expressed as the percentage sensitive.

It is not uncommon for a physician to ignore sensitivity results on both hospital and office patients when his personal drug of choice is not indicated as best by the laboratory test. The discrediting of laboratory results, subsequent use of a favorite antibiotic, and other abuses of antibacterial therapy are among the factors implicated in the etiology of organismal resistance. Important among these other abuses of antimicrobial therapy are the delay in institution of therapy, inadequate dosage, an insufficient period of therapy, and failure to individualize the pathological physiology of each infectious process.

As stated in the introduction, certain individual groups are obligated to make available to practicing physicians such data as those on the changing susceptibility of infectious agents and the local status of the antimicrobials

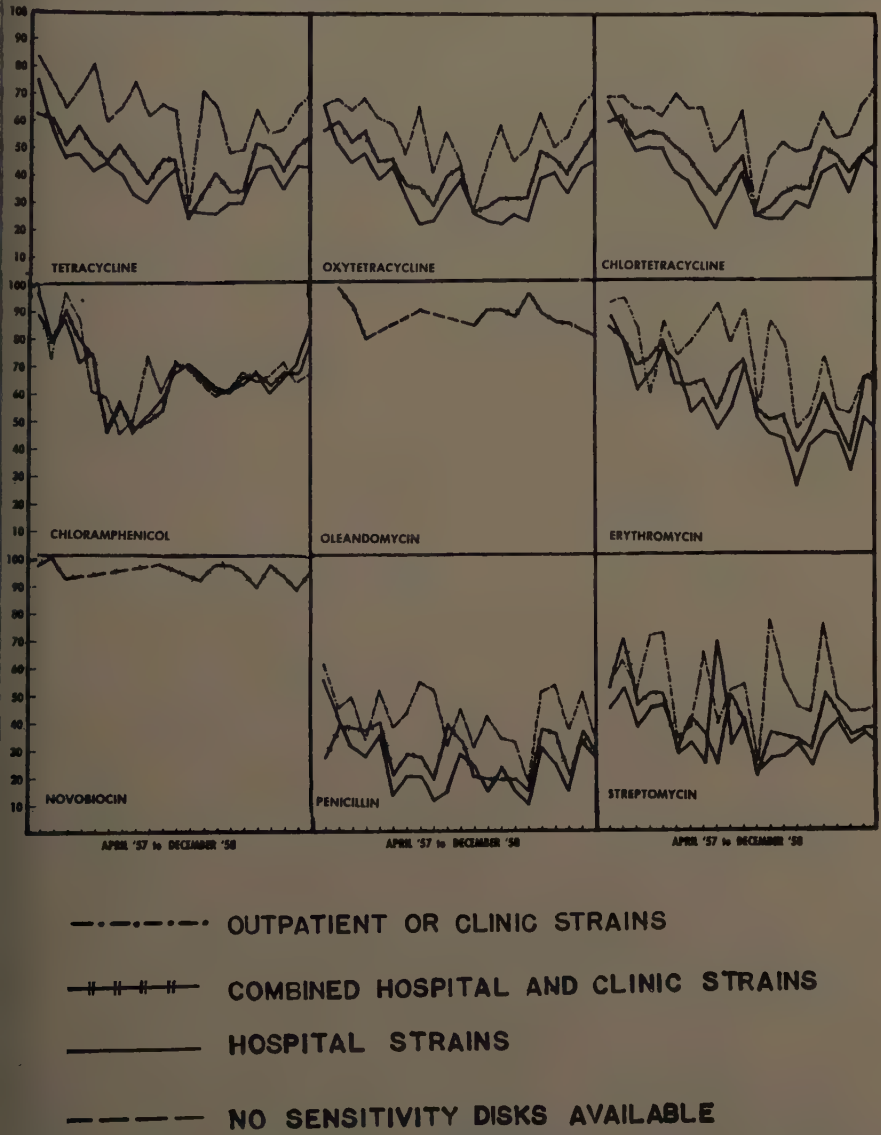


FIGURE 2. Comparison of varying susceptibility patterns of clinic and hospital coagulase-positive staphylococci (FIGURE 1). Susceptibility is expressed as the percentage sensitive.

used to combat them. The average physician, because of his work load and unfamiliarity with such problems, constantly needs guidance and information on current conditions. Our experience with respect to the degree of acceptance of our findings in recent months has been most gratifying. The compilation of the local current status of antimicrobial laboratory sensitivity results must

come from the hospital pathologist (if available) or the clinical bacteriologist. If these two sources are unavailable, the medical technologist responsible for bacteriology in the community hospital can easily tabulate such information. The dissemination of this material could be handled through the local medical society.

The need for immediate recognition of wider application of clinical bacteriological procedures has received scattered acknowledgment. Considerable progress has been made by some communities, and there is one important step that would aid in a more rapid and widespread achievement of this goal. This would involve a reorganization of and re-emphasis in the teaching of clinical bacteriology to current medical trainees.

Because the disk method is the most practicable for our routine needs, as it is with the majority of other routine clinical laboratories, we try constantly to improve the technique. At present we are engaged in a study in which approximately 1000 clinically isolated pathogens of all types will be subjected to triplicate tube-dilution studies and triplicate disk studies. The disk studies will include comparisons on different media. Currently, disk sensitivity re-

TABLE 2

COMPARISON OF DISK AND TUBE–DILUTION TEST RESULTS EMPLOYING 50 MICROORGANISMS

Percentage sensitive	Tetracycline	Chloramphenicol	Oleandomycin	Novobiocin	Penicillin	Streptomycin	Kanamycin
Disk	36	84	56	56	28	24	92
Tube	52	76	48	48	36	32	92

porting by clinical laboratories varies from institution to institution. Reported results may be based on the use of (1) low-concentration disks alone, (2) high-concentration disks alone, or (3) comparison of results from both high- and low-concentration disks. This study will include currently available disks, as well as those subject to anticipated Food and Drug Administration controls. From this study we expect to reveal, among other significant data, that different degrees of correlation exist between different groups of organisms of the same genera and species and between different antibacterials under both controlled and routine methods of study. It is felt necessary to conduct a study of this magnitude in order to give statistically significant data. The all-important matter of *in vitro* and *in vivo* correlation will be given considerable attention.

The data in TABLE 2 represent the final tabulations, expressed as the percentage sensitive, of a comparison between the tube and the disk tests, employing 50 microorganisms. The methods employed in these tests were described in a previous publication.[3] Presence of a zone of inhibition around the disk and a minimum inhibitory concentration of 12.5 μg./ml. (tube test[4]) was accepted as indicating sensitivity. With the exception of those on tetracycline, these data indicate a variation between the 2 tests of less than 10 per cent.

It is stressed, however, that these figures constitute results on only 50 organisms and that definite conclusions will be withheld until the availability of more data allows analysis with statistically significant numbers.

Sulfonamide Sensitivity Studies

Our preliminary sulfonamide studies were designed primarily to study the correlation of the tube-dilution and the disk-plate tests and to compare results obtained in the disk-plate test using several types of agar and blood combinations. Tube-dilution studies were performed using S-R medium (Difco) and trypticase soy broth (BBL). The disk tests were performed on agar plates prepared from trypticase soy agar (BBL) and Mueller-Hinton agar (BBL), either plain or prepared as blood plates using 5 per cent citrated human blood-bank blood or washed sheep erythrocytes.

A partial breakdown of these data, presented in TABLE 3, indicates to us that the simple choice of an agar, even though generally recommended for

TABLE 3

PERCENTILE SENSITIVITY RESULTS OF THREE SULFONAMIDE DISK TESTS PERFORMED ON COMBINATIONS OF MUELLER-HINTON AND TRYPTICASE SOY AGAR

Sulfonamide		T-S Human blood*	M-H Human blood	T-S Sheep blood†	M-H Sheep blood	T-S Plain	M-H Plain
Madribon (1.0 mg.)	R	92	92	92	92	92	92
	S	8	8	8	8	8	8
Sulfadiazine (1.0 mg.)	R	92	92	92	92	92	92
	S	8	8	8	8	8	8
Triple sulfa (1.0 mg.)	R	92	92	92	92	92	92
	S	8	8	8	8	8	8

* Citrated human blood bank blood.
† Washed suspension on sheep erythrocytes.

sulfonamide sensitivity testing, is not in itself an assurance of superior test results. Although these studies are still in progress, the findings thus far tend to confirm our previous observation of extremely low percentile levels of sulfonamide sensitivity[1] and poor correlation between the tube- and disk-test results (to be reported later), regardless of the medium used. None of the agar forms tested, including Mueller-Hinton, demonstrated a superior suitability for the disk test when performed in a manner standard for antibiotic testing. These data, coupled with a long-standing study of material in the clinical bacteriology laboratory, do indicate, however, that the percentile level of disk-test sensitivities can often be increased by either of the following 2 methods: (1) altering the criteria for determining disk-test sensitivity—for example, accepting as sensitive those organisms that produce zones of complete or partial inhibition of growth, and (2) the use of disks of higher than normal concentration.

The data in TABLE 4 show that this change in test interpretation will place in the sensitive class many organisms that were previously interpreted as re-

sistant. This change in end result now demonstrates a difference in the results obtained on the various media. Plain trypticase soy agar indicates higher levels of sensitivity than were observed on plain Mueller-Hinton agar, while the addition of citrated human blood-bank blood to the Mueller-Hinton agar produced levels that are generally equal to or higher than both of the former.

TABLE 4

COMPARATIVE SENSITIVITY RESULTS OF THREE SULFONAMIDE DISK TESTS BASED ON STANDARD* AND ALTERED† CRITERIA OF TEST INTERPRETATION

Sulfonamide	Sensitivity criteria	T-S Human blood	M-H Human blood	T-S Sheep blood	M-H Sheep blood	T-S Plain	M-H Plain
Madribon (1.0 mg.)	S*	8	8	8	8	8	8
	A†	36	64	40	36	48	44
Sulfadiazine (1.0 mg.)	S	8	8	8	8	8	8
	A	36	36	32	32	32	36
Triple sulfa (1.0 mg.)	S	8	8	8	8	8	8
	A	36	40	36	32	32	36

* Sensitivity: complete inhibition.
† Sensitivity: partial or complete inhibition.

TABLE 5

COMPARATIVE SENSITIVITY RESULTS OF TWO CONCENTRATIONS OF TWO DISK TESTS BASED ON STANDARD* AND ALTERED† CRITERIA OF TEST INTERPRETATION

	Sensitivity criteria	T-S Human blood	M-H Human blood	T-S Sheep blood	M-H Sheep blood	T-S Plain	M-H Plain
Sulfadiazine							
1.0 mg.	S*	8	8	8	8	8	8
	A†	36	36	32	32	32	36
0.3 mg.	S	8	8	8	8	8	8
	A	24	28	20	16	16	28
Gantrisin							
2.0 mg.	S	24	24	20	20	40	24
	A	60	68	52	56	72	56
0.3 mg.	S	8	8	8	8	8	8
	A	36	48	28	32	36	32

* Sensitivity: complete inhibition.
† Sensitivity: partial or complete inhibition.

This observation has been made by others, since Mueller-Hinton blood plates are routinely used for this purpose by several laboratories.[2]

Data presented in TABLE 5 indicate that the standard performance of the disk-plate test does not demonstrate a difference between low- and high-concentration disks. The altered criteria of interpretation, however, do show higher sensitivity percentages with the more concentrated disk. If the disk strength is sufficiently increased, as in the case of Gantrisin, a difference can

be seen in the results obtained with the low- and high-concentration disks, even in a test performed by a standard method. When these tests are interpreted by the altered criteria, the over-all sensitivity percentages are increased and give evidences of medium superiority.

Many physicians have obtained a rate of response to the sulfonamide drugs significantly higher than was indicated from disk-plate sensitivity tests. These altered criteria for the interpretation of the sulfonamide disk test, in producing higher indications of sensitivity, may offer a partial solution to the problem. We believe that these results would provide a higher degree of correlation between clinical result and probable efficacy as indicated by the disk test. Definite statements in this matter must, of course, await the analysis of a specifically designed clinical laboratory study.

Definite conclusions on the agar medium of choice for the disk-plate test will be withheld until completion of these studies, but thus far it is evident that the plain Mueller-Hinton agar is not unequivocally the medium of choice.

Summary

A preliminary study covering a 21-month period and showing susceptibility patterns of 7000 Gram-positive cocci is presented.

Graphic illustration of monthly and seasonal variations in susceptibility of a large group of pathogenic staphylococci to a selected group of antibiotics is also presented. Considerable variation is shown in the susceptibility of pathogenic staphylococci isolated from the outpatient and the hospital patient toward the same antibiotic during the same month. These findings tend to discredit the practice of depending upon past experience, clinical judgment, or both as sole criteria for selection of antibacterial therapy.

Preliminary data relative to a comprehensive study on disk-method and tube-dilution sensitivity testing with *in vivo* correlation is discussed.

A step toward the restoration of the clinical use of sulfonamides is presented. Preliminary studies indicate that a much closer correlation between *in vitro* sulfonamide sensitivity testing and *in vivo* response can be achieved by the alteration of interpretive criteria.

References

1. Leming, B. H., Jr. & C. Flanigan, Jr. 1959. Correlation of sensitivity patterns of antimicrobial agents by the disc-plate method; a preliminary study involving 5600 Gram-positive cocci. Antibiotics Ann. 1958–1959. : 977.
2. Hubble, R. H. Chicago State tuberculosis sanatorium, Chicago, Ill. Personal communication.
3. Flanigan, C., Jr., B. H. Leming, Jr. & J. Lawrence. 1959. A study of possible *in vivo* oleandomycin resistance increase in *Staphylococcus aureus* (a preliminary report). Antibiotics Ann. 1958–1959. : 414.
4. Suter, L. S., & E. W. Ulrich. 1959. Routine bacterial sensitivity studies. Antibiotics & Chemotherapy. **9:** 1.

TREATMENT COMPLICATIONS IN THE UPPER RESPIRATORY TRACT: A CONSIDERATION OF THE BACTERIAL FLORA OF THE UPPER RESPIRATORY TRACT IN THE NORMAL, INFECTED, AND TREATED PATIENT

Thomas D. Michael
University of Maryland School of Medicine, Baltimore, Md.

Exact knowledge of bacterial flora of the upper respiratory tract in health and disease would be of immeasurable aid in the treatment of infections of that region. The number of bacterial cultures of the upper respiratory tract obtained each year in a large general hospital (2000 to 3000 at the University of Maryland Hospital) indicate that a respectable number of physicians regard knowledge of the bacterial flora of the upper respiratory tract as indispensable, or at least desirable, in the determination of proper therapy. However, the interpretation of information obtained from such studies remains obscure. The paucity of exact data on the normal flora renders the task of interpreting the "abnormal" arbitrary at best. Unquestionably, potentially pathogenic bacteria are constantly present in the upper respiratory tract of most if not all normal individuals. The nasopharynx and pharynx are the most common locations for these potential pathogens, with some variation existing between these two sites.[1] The location of the point at which these potential pathogens become of clinical significance constitutes a tantalizing enigma. Pure cultures are uncommon and are seen in the clinically well and the symptomatic individual. Pure cultures of potentially pathogenic staphylococcus may in fact emerge during antimicrobial therapy directed at infection elsewhere[2, 3] without subsequent development of significant upper respiratory tract symptoms.

There are few points of general agreement concerning the bacterial flora of the normal upper respiratory tract. The presence of large numbers of staphylococci in the normal vestibule and the relative sterility of the nasal cavity proper are conceded.[4] However, when the nasopharynx is considered, there is an immediate and striking divergence of findings. The *Diplococcus pneumoniae* (pneumococcus) has been reported in the nasopharynx of normal controls in percentages varying from 3.5 to 48,[5-8] while in infection some have felt that there was a significant increase in pneumococcal isolates,[9, 10] and others have shown only a moderate increase.[6] The β-hemolytic *Streptococcus* has been reported as varying from less than five[7] to more than 20 per cent,[6] and the *Staphylococcus pyogenes* var. *aureus* from thirty-five[8] to 3.4.[6] *Hemophilus* is even more striking, varying from fifteen[7] to less than 1 per cent.[6] To complicate the problem further, the *Neisseria* and the diphtheroid groups have been ignored by some[8] as possible upper respiratory tract pathogens, while being considered worthy of comment and investigation by others.[11]

The significance of a single culture is a dilemma resolved with no greater ease than the previous conflicting statistics. A mixed culture is the rule in the normal, infected, and treated patient. The primacy as to growth is fre-

quently shared between two and even three bacteria. By contrast, a pure culture of pneumococcus is occasionally seen in a symptomless individual.

Recently, the evaluation of potentially pathogenic staphylococci has been of particular concern to physicians treating infections of the upper respiratory tract. Cultures containing this organism are particularly difficult to interpret, for such bacteria have been demonstrated in the nasopharynx of premature infants,[2] in a significant number of children,[7, 8, 12] and in a high percentage of normal adults.[5, 6] There is evidence, however, that there has been no real change in the problem of *Staphylococcus* carriers.[13] The series reported by Molomut *et al.*,[11] which utilized only patients with evidence of chronic upper respiratory infection, demonstrated 5.8 per cent potentially pathogenic *Staphylococcus*, which is considerably below that reported in several normal series. It has been stated[3, 14, 15] that *S. pyogenes* var. *aureus* has no significant implication for the carrier. The failure of anyone to demonstrate any significant fluctuation in the percentage of these organisms in upper respiratory infection would appear to substantiate the validity of this statement. The exception could certainly occur if this organism became loculated in an appendage of the upper respiratory tract. The emergence of an increased percentage of resistant staphylococcal strains in hospitalized patients, particularly those under antibiotic therapy,[3, 14] has not been accompanied by any corresponding increase in upper respiratory infections. There is a significant percentage of carriers of potentially pathogenic staphylococci in the nonhospital contact population,[3] as well as a small but definite cross-inoculation involving families of discharged hospital patients. Once again, there is no evidence of a corresponding increase in upper respiratory tract infection. *Staphylococcus*, despite its frequent presence, does not appear to be the etiological agent in a significant number of upper respiratory tract infections. Reserve should be exercised in designating this organism as a responsible agent for infection.

If *Staphylococcus* can be dismissed as a common agent of upper respiratory tract infections, the remaining organisms of principal concern are the pneumococcus, *Streptococcus*, both hemolytic and nonhemolytic, and *Hemophilus*. The pathogenicity of *Neisseria* (which certainly abounds in the nasopharynx), the diphtheroids, and the Gram-negative bacilli is undecided. The latter two groups are, however, not of great frequency and appear to be primarily the end product of prolonged antibiotic therapy in hospitalized patients.

One thousand cultures of the upper respiratory tract were examined in the hope of finding variations from the normal, which would be indicative of infection. An attempt was also made to establish variations that might typify therapeutic failures with antimicrobials. Studies of the nasal vestibule and nasal cavity proper were not included. The limited studies of Goldman[5, 12] suggest that further consideration of the flora of the nasal cavity proper might be of clinical value. Cultures from 100 patients free of upper respiratory tract infection, 112 patients responding inadequately to antimicrobial therapy, and 788 patients with evidence of acute upper respiratory infection were included in the study. Cultures were done by the conventional plating on blood agar, for it was hoped to find a criterion of clinical significance applicable under circumstances generally available to the practicing physician. Identification was by smear, colony morphology, and Gram's stain. The significance of the

findings was judged with the use of χ squared, taking a value of p at 0.05 or less as significant.

The number of statistically significant findings was disappointingly few. The marked seasonal fluctuation of β-hemolytic *Streptococcus* was again confirmed. The β-hemolytic *Streptococcus* is indeed uncommon in fall and early winter, but shows a marked resurgence starting in March, continuing through April and May. There was a significant increase in pneumococcus in the infected, opposed to the normal, controls (58.1 as opposed to 46 per cent) and a corresponding decrease in these bacteria in treated patients (58 to 36 per cent). Despite the reduction of pneumococcus in treated patients, it still remained by far the predominant organism. In a recent study Willard[8] noted the increased incidence of heavy growth of pneumococcus in patients with active upper respiratory tract infection when compared with normal controls. Unfortunately, this finding could not be confirmed. There was a definite emergence of Gram-negative bacilli with continuation of antibiotic therapy. These bacteria remained a relatively small percentage of the total and were the predominant organisms in only 2.6 per cent of infected and treated patients.

No statistically significant decline was noted in the percentage of hemolytic *Staphylococcus aureus* with antibiotic therapy. The percentage of *Hemophilus* species encountered in this series was so small (1.3 per cent of all cultures) that no positive conclusions were possible. Surprisingly, in 7.5 per cent, *Neisseria* constituted the primary growth, and was present also in 33.9 per cent of all cultures. The growth decreased with short-term antibiotic therapy, but appeared to return to its initial percentage when this treatment was continued.

Pure cultures were a rarity in normal, infected, and treated patients, and the presence of a pure culture per se does not automatically implicate that organism as pathogenic. There was no variation in the number of different organisms found in a single culture among the three groups studied. Mixed cultures were the rule, frequently with two and sometimes three different organisms showing equal growth. No significant variations were found in the flora of patients not responding to initial antimicrobial therapy. The previously mentioned decrease in percentage of pneumococcus and a corresponding decrease in β-hemolytic *Streptococcus* with the emergence of a small number of Gram-negative bacilli were the only positive findings. As now becomes quite evident, the purpose of the study remained completely unfulfilled. However, as the examination of cultures and related medical literature continued, several points of speculative interest arose.

It is quite evident that no significant number of pathogens foreign to the upper respiratory tract appears during infections. In infection, both treated and untreated, the organisms remain the same as those that can be cultured from any normal nasopharynx with serial examinations. If the hemolytic *Staphylococcus aureus* can be considered to be seldom of clinical significance in upper respiratory infection, the remaining bacteria are those that are not characterized by the development of resistant strains. From a bacteriological standpoint alone, good clinical response would be expected, regardless of which antimicrobial agent was chosen for therapy. However, failures do occur. In the upper respiratory tract the cause of these failures and subsequent complications would not appear to lie primarily in the choice of antibacterial agent,

and the solution is not in haphazard selection from a profusion of antimicrobial agents.[16] Unfortunately, it is evident that a culture will frequently fail to clarify the reason for therapeutic failure.

The upper respiratory tract has appendages that are ideally constructed for loculation of infection, and it appears that persistence of infection results primarily from failure to restore adequate drainage from these loculated areas rather than in the failure of the chosen antimicrobial agent to perform its assigned task. An increase in therapeutic success with associated decrease in complications would appear to be dependent upon assurance of adequate drainage of all involved areas rather than the selection of a particular antibacterial agent.

There have been increasing pleas to avoid broad-spectrum antibiotic therapy where feasible in an effort to control the number of strains of resistant hemolytic *S. aureus*. The bacteriological findings in the upper respiratory tract strongly suggest that good therapeutic results can be expected from the use of sulfonamide therapy. What is frequently interpreted as a failure for sulfonamide therapy may in reality indicate the establishment of inadequate drainage from the area of loculated infection.

References

1. Plummer, N. 1949. A comparison of the bacterial flora of the pharynx and nasopharynx. Am. J. Hyg. **50:** 331.
2. Stoppelman, M. R. H. 1954. Effect of antibiotics on nasopharyngeal flora of premature infants. Am. J. Diseases Children. **88:** 339.
3. Goslings, W. R. O. & K. Buchli. 1958. Nasal carrier rate of antibiotic-resistant staphylococci. A.M.A. Arch. Intern. Med. **102:** 691.
4. Medical Research Council. 1931. A System of Bacteriology. **8.** His Majesty's Stationery Office. London, England.
5. Goldman, J. L. 1950. Bacteriologic and clinical interpretation of the flora of the nose and nasopharynx in adults. Ann. Otol. Rhinol. & Laryngol. **59:** 156.
6. Kolmer, J. A., A. Bondi & C. Schellinger. 1948. The bacterial flora of the nasopharynx in relation to the common cold. A.M.A. Arch. Otolaryngol. **47:** 571.
7. Yang, H. S. 1941. Nasal flora of the children in a day nursery. Am. J. Diseases Children. **61:** 262.
8. Willard, C. Y. & A. E. Hansen. 1959. Bacterial flora of the nasopharynx in children. A.M.A. J. Diseases Children. **97:** 318.
9. Kneeland, Y., Jr. 1949. The relationship of bacteria to the common cold. Bull. N. Y. Acad. Med. **25:** 534.
10. Willard, C. Y. & A. E. Hansen. 1958. Influence of previous antimicrobial agents on the nasopharyngeal flora of children. Antibiotics Ann. 1957–1958. : 365.
11. Molomut, N., S. J. Prigal, A. Haber & H. Hirsch. 1953. Action of combinations of sub-effective doses of antibiotics on bacteria isolated from patients. Antibiotics & Chemotherapy. **3:** 249.
12. Goldman, J. L., S. M. Bloom & C. Herschberger. 1954. Bacteriologic and clinical interpretation of the flora of the nose and nasopharynx in children. J. Pediat. **44:** 299.
13. Gillespie, E. H., E. A. Devenish & S. T. Cowan. 1939. Pathogenic staphylococci. Lancet. **2:** 870.
14. Lepper, M. H., H. F. Dowling, G. G. Jackson & M. M. Hirsch. 1953. Epidemiology of penicillin and aureomycin-resistant staphylococci in a hospital population. A.M.A. Arch. Intern. Med. **92:** 40.
15. Lepper, M. H., G. G. Jackson & H. F. Dowling. 1955. Characteristics of the micrococcal nasal carrier state among hospital personnel. J. Lab. Clin. Med. **45:** 935.
16. Karelitz, S. 1953. Choice of an antibiotic. J. Pediat. **42:** 478.

LABORATORY AND CLINICAL STUDIES WITH SULFADIMETHOXINE: A PRELIMINARY REPORT

Sydney M. Finegold, Zoya Kudinoff, Harry O. Kendall, Virginia E. Kvinge
Department of Medicine, Wadsworth Hospital, Veterans Administration Center, and Department of Medicine, University of California Medical Center, Los Angeles, Calif.

A new sulfonamide, sulfadimethoxine (Madribon*), has been found to exert protective activity comparable to that of sulfadiazine and sulfamethoxypyridazine and superior to that of sulfisoxazole in a number of experimental infections produced by Gram-positive and Gram-negative organisms[1] and in *in vitro* antibacterial studies. The drug is absorbed rapidly following oral administration; it reaches high plasma concentrations in 4 to 6 hours, and effective plasma concentrations are maintained for at least 24 hours following single daily oral doses.[2-4] Only about 10 per cent of the drug in the plasma is in the conjugated form. The drug is excreted slowly in the urine, chiefly as a highly soluble glucuronide. Spinal fluid levels are low.

Sulfadimethoxine has been well tolerated, and the toxic potential appears quite low.[1-5] Clinical data have been reported by several investigators[3-5] with generally good results in a variety of infections of mild to moderate severity. Unfortunately a number of the results with infections treated have not been substantiated bacteriologically.

The present study was undertaken to evaluate sulfadimethoxine clinically in a group of hospitalized adults; certain laboratory data are also reported.

Materials and Methods

Thirty-one adults were treated with sulfadimethoxine for a variety of infections and to obtain pharmacological data. Twenty-eight of these patients were hospitalized. Twenty-seven patients received an initial oral dose of 2 gm. followed by single daily doses of 1 gm. Two patients received 2 gm. daily and 2 patients received an initial dose of 1 gm. followed by 0.5 gm. daily. The patients were treated for from 5 to 60 days (average 19 days); 7 received the drug for 4 weeks or longer. The types of cases treated are noted in TABLES 3 and 4.

Blood was drawn 8 hours following the morning dose of drug, and urine specimens were obtained at the same time without attempting to collect urine over a given period of time. Blood and urine levels of free sulfadimethoxine were determined by a modified Bratton-Marshall technique.[6]

In addition to chemical determination of drug levels, 10 serum specimens obtained at 8 hours following a dose were serially diluted (twofold dilutions) and tested against the infecting organism from the corresponding patient. The latter tests were set up in triplicate; 2 of the tests were set up with equal amounts of a 24 hour broth culture diluted 1:100 (one set containing para-aminobenzoic acid [PABA] to give a final concentration of 5 mg./100 ml.) and the third was set up with a 10^{-4} dilution of a similar broth culture without

* Hoffmann-La Roche.

PABA. The broth used throughout was identical in composition to commercially available Mueller-Hinton medium except for the elimination of the agar. Serum and growth controls were included with each test, and tests were incubated for 24 hours at 37° C. before being read.

Appropriate bacteriological cultures were taken prior to, during, and following treatment with sulfadimethoxine. In the case of urinary tract infections, quantitative urine cultures were used routinely. *In vitro* sensitivity tests of two types were set up with pathogenic organisms recovered from the patients. Disk-sensitivity tests were performed using Mueller-Hinton agar plates and 1.0 mg. sulfadimethoxine disks. Plate dilution sensitivity tests were set up using the following final concentrations of sulfadimethoxine in Mueller-Hinton agar plates: 1.0, 0.5, 0.25, 0.125, 0.0625, 0.0312, 0.0156, 0.0078, and 0.0039 mg./ml. These plates, plus a control plate, were inoculated with a standard loopful of a 24-hour brain-heart infusion broth culture, incubated for 24 hours at 37° C., and then read. A total of 26 strains of organisms isolated from patients being treated with sulfadimethoxine was tested by the above techniques; included were 6 strains of *Klebsiella-Aerobacter*, 5 of *Staphylococcus aureus*, 4 of *Escherichia coli*, 3 of *Pseudomonas aeruginosa*, 2 each of *Proteus mirabilis*, *P. vulgaris*, and *P. rettgeri*, and 1 each of *Nocardia asteroides* and intermediate coliform. In addition to these 26 strains, 40 additional strains of bacteria isolated from clinical material in the last 6 months were tested by the two techniques discussed above. Included in the latter group were 5 strains each of *Staph. aureus*, *E. coli*, *Klebsiella-Aerobacter*, *Pseudomonas*, and enterococci, 4 of paracolons, 3 of *Alcaligenes fecalis*, and 2 each of *P. mirabilis*, *P. vulgaris*, *P. morgani*, and *P. rettgeri*.

In two patients receiving 2 gm. of sulfadimethoxine daily, quantitative bacteriological studies on stool specimens were obtained prior to the institution of treatment and 3 days thereafter. Serial tenfold dilutions of stools were transferred to appropriate media and incubated aerobically and anaerobically (Brewer anaerobic jar).

Complete blood counts, urinalyses, and serum creatinine determinations were obtained before and after treatment with sulfadimethoxine and at regular intervals (at least once or twice weekly) during treatment. Other laboratory studies were done as indicated.

Results

Laboratory data. The results of the chemical determination of free sulfonamide blood levels are noted in TABLE 1. The over-all average 8-hour blood level in 19 determinations was 5.49 mg./100 ml. The data as presented do not indicate any evidence of cumulative effect, nor does analysis of levels taken on more than one occasion in the same patient suggest such an effect. It should be noted that the spread was rather wide, namely, 2.00 to 11.83 mg./100 ml.

Urine levels at 8 hours were done in 6 patients; the levels varied from 50.26 to 224.13 mg./100 ml.

The 10 sera serially diluted and checked for antibacterial activity against the corresponding infecting organism yielded virtually negative results; no in-

hibition was noted with the heavier inoculum. In only 1 case was there inhibition of the organism with the lighter inoculum; this inhibition occurred only to a serum dilution of 1:4 and was not noted in the set containing PABA. However, only 1 of the 10 patients whose sera were tested had a favorable clinical and bacteriological response; this was not the patient showing some activity in the serum.

TABLE 1

BLOOD LEVELS (MG./100 ML.) OF FREE SULFADIMETHOXINE 8 HOURS FOLLOWING SINGLE DAILY DOSE OF 1 GM.*

Days of therapy			
1 to 2	3 to 5	7 to 10	More than 10
7.20	4.99	4.53	7.67
4.46	6.32	11.83	5.90
3.50	3.53	2.00	5.80
2.00	9.70	2.98	
6.73	6.23		
3.53	5.44		
Average 4.57	6.04	5.25	6.23

Over-all average blood level (19 determinations) 5.49.
* All patients received 2 gm. the first day, then 1 gm. daily.

TABLE 2

EFFECT OF SULFADIMETHOXINE ON NORMAL HUMAN FECAL FLORA (Patients Received 2 gm. Daily for 3 Days)

Organism	Patient No. 1, control	Patient No. 1, 3 days	Patient No. 2, control	Patient No. 2, 3 days
Escherichia coli	10^{7}*	0	10^{9}	10^{9}
E. intermedium	10^{3}	0	0	0
Klebsiella-Aerobacter	10	10^{5}	0	0
Enterococcus	10^{7}	10^{7}	10^{9}	10^{10}
Streptococcus viridans	10^{5}	10^{5}	0	0
Staphylococcus epidermidis	0	0	10^{9}	10^{9}
Bacteroides	10^{7}	10^{8}	10^{9}	10^{9}
Lactobacillaceae	10^{5}	10^{5}	10^{9}	10^{9}

* Number of organisms/gm. wet stool.

The 66 strains checked for *in vitro* sensitivity to sulfadimethoxine were virtually uniformly resistant by the techniques employed in this study. Only 1 strain (a paracolon) showed sensitivity by the disk technique; all strains were resistant to at least 1 mg./ml. by the plate dilution technique. Nevertheless, many of the patients whose strains appeared resistant *in vitro* responded well both clinically and bacteriologically, as is noted below in TABLES 3 and 4.

The effect of sulfadimethoxine on the fecal flora of 2 patients is noted in TABLE 2. Note that there was no change whatever in the fecal flora of 1 patient, and that the only change in the second patient was replacement of *Escherichia* with *Klebsiella-Aerobacter*.

Clinical data. The results of therapy are shown in TABLES 3 and 4. In

certain cases it was not possible to evaluate the effectiveness of the drug because of questionable diagnosis or because of insufficient bacteriological data; at times, repeat cultures taken just before therapy was initiated were negative, so that no evaluation could be made.

With regard to genitourinary infections, the best results were obtained in infections due to *E. coli*; 3 patients had good clinical and bacteriological re-

TABLE 3
CLINICAL RESULTS WITH SULFADIMETHOXINE
Cystitis and/or Pyelonephritis

Infecting organism	Response		
	Good*	Poor	Indeterminate
Escherichia coli	3	1† 2‡	1
Intermediate coliform		1	
Klebsiella-Aerobacter	1	1 1†	
Paracolon coliforme	1		
Pseudomonas		2	
Proteus mirabilis		1	
P. vulgaris			1
P. mirabilis and *E. coli*		1†‡	
P. mirabilis, *E. coli*, and *P. rettgeri*		1†	

* Clinical and bacteriological response.
† Original organism eliminated, but replaced by another.
‡ Clinical response, but no bacteriological response.

TABLE 4
CLINICAL RESULTS WITH SULFADIMETHOXINE
Miscellaneous Infections

Infection	Response		
	Good	Poor	Indeterminate
Soft tissue infection (staphylococcal)	2	1	2
Pneumonitis	1		1
Lung abscess		1	
Nocardiosis (pneumonitis and empyema)	1		
Nonspecific urethritis		1	
Abscess, tooth socket (*Actinomyces*)	1		

sponses, 2 others showed clinical improvement (as judged from temperature, evidence of pyuria, and other symptoms) without elimination of the *E. coli*, and in 1 patient *E. coli* was eliminated but replaced by *Klebsiella-Aerobacter* and intermediate coliforms. The results were generally less satisfactory in urinary tract infections due to other organisms, particularly those due to *Pseudomonas* and *Proteus*.

Most of the patients with genitourinary infections in this series had some underlying mechanical problem such as lower urinary tract obstruction, renal calculi, and chronic pyelonephritis. It is likely, therefore, that continued

follow-up of the patients with good clinical and/or bacteriological responses will reveal a significant percentage of relapses. It is interesting that the results were at least as good in patients with chronic as in those with acute infections in this series.

As indicated above, a good clinical response was sometimes obtained in the absence of a bacteriological response; in patients with chronic infection superimposed on a mechanical problem not susceptible to correction, such a response must still be considered good. For example, one of our patients had a neurogenic bladder and a chronic infection with *P. mirabilis* and *E. coli*. Prior to sulfadimethoxine therapy the patient had severe discomfort requiring codeine regularly; although quantitative urine cultures failed to reveal any change in the urinary flora following treatment, the patient immediately experienced total relief of discomfort and was very grateful.

Table 4 shows results of sulfadimethoxine therapy of some miscellaneous infections. The number of infections treated is too small to permit the drawing of any conclusions, but one case is worthy of special comment. A young physician had been troubled with furuncles over a period of many months. He had no known underlying condition such as diabetes. He had taken erythromycin and novobiocin in the past with no results (new furuncles appeared while he was on these drugs). He was placed on sulfadimethoxine when two new furuncles appeared. The response (without drainage or other adjunctive therapy) was prompt; no new furuncles appeared during the 6 weeks that he remained on the drug, and none has appeared in the month subsequent to discontinuing therapy.

Toxicity and tolerance. One patient had moderate nausea and vomited once every few hours after the first dose of sulfadimethoxine; she continued to take the drug for another 13 days with no further difficulty. One patient had mild urticaria after 3 weeks of therapy; the drug was again initiated 2 days later and was continued for another 9 days without recurrence of the urticaria.

Two patients had eosinophilia of 7 to 11 per cent on 1 and 2 occasions, respectively; there were no associated symptoms or findings.

There were no other subjective or objective evidences of intolerance or toxicity; the serial laboratory tests failed to reveal any abnormalities possibly attributable to sulfadimethoxine therapy other than the eosinophilia mentioned above.

Discussion

The blood levels of sulfadimethoxine obtained in this study are comparable to those obtained by others.[2-4] If it is true for sulfadimethoxine (as for the similar compound, sulfamethoxypyridazine) that all of the sulfonamide present in whole blood is generally found in the plasma, then whole blood levels would be approximately one half those of plasma.[3] The variability in blood levels from person to person on similar dosages suggests the desirability of individualizing dosage on the basis of blood level studies.

The remarkable ineffectiveness of sulfadimethoxine *in vitro* under the conditions tested contrasts with the good clinical and bacteriological response obtained in the treatment of some of the patients whose organisms appeared

resistant. The lack of reliability of *in vitro* sensitivity testing with sulfonamides in general is well known.

The relatively minor change in the fecal flora effected by this drug is worthy of note and indicates considerably less likelihood of superinfections resulting from the replacement of normal flora than with many other chemotherapeutic agents.

The clinical results obtained were roughly comparable to those noted with sulfamethoxypyridazine in the treatment of urinary tract infections.[7] It appears that sulfadimethoxine is most consistently active against *E. coli*, but will also be useful in some infections caused by other organisms. Ordinarily, it should be used only in infections of mild to moderate severity. Certainly, sulfadimethoxine is an excellent sulfonamide with some unusual and interesting properties; nevertheless, it is subject to the limitations of the sulfonamide drugs in general as far as its range of usefulness is concerned.

The incidence of side effects and toxicity has been low in other series[2-5] and was low in the present study. Serious reactions to sulfadimethoxine have not been reported as yet; nevertheless, it is very important to withhold judgment on this point until many more cases have been carefully followed. As Ross and his co-workers[3] have pointed out, there were only a few minor side effects noted from the structurally similar drug sulfamethoxypyridazine, initially, and subsequently an occasional patient has been shown to exhibit a dangerous reaction.

Summary

A preliminary report on laboratory and clinical studies with sulfadimethoxine is given. Although the *in vitro* results were poor, as is often the case with sulfonamides, good clinical and bacteriological results were obtained in the treatment of some infections, notably those due to *E. coli*. Single daily doses of 1 gm. in adults proved effective. The drug is an effective sulfonamide subject to the limitations of sulfonamides in general, as far as its range of usefulness is concerned. Toxicity was negligible in this small series, and the drug was well tolerated for prolonged periods.

Acknowledgment

The sulfadimethoxine employed in this study, both for laboratory and clinical purposes, was supplied by John L. Spencer of Hoffmann-La Roche Inc., Nutley, N. J.

References

1. Schnitzer, R. J., W. F. DeLorenzo, E. Grunberg & R. Russomano. 1958. Chemotherapeutic studies with 2,4-dimethoxy-6-sulfanilamido-1,3-diazine. Proc. Soc. Exptl. Biol. Med. **99:** 421.
2. Boger, W. P. 1959. A new long-acting antibacterial sulfonamide, 2,4-dimethoxy-6-sulfanilamido-1,3-diazine: a comparative study. Antibiotics Ann. 1958–1959. : 48.
3. Ross, S., J. R. Puig & E. A. Zaremba. 1959. Sulfadimethoxine, a new long-acting sulfonamide. Antibiotics Ann. 1958–1959. : 56.
4. Townsend, E. H., Jr. & A. Borgstedt. 1959. Preliminary report of clinical experience with sulfadimethoxine, a new long-acting sulfonamide. Antibiotics Ann. 1958–1959. : 64.

5. Leming, B. H., Jr., C. Flanigan, Jr. & B. R. Jennings. 1959. Clinical evaluation of sulfadimethoxine (Madribon), a wide-spectrum antibacterial. Antibiotic Med. & Clin. Therapy. **6**(Suppl. 1): 32.
6. Bratton, A. C. & E. K. Marshall, Jr. 1939. A new coupling component for sulfanilamide determination. J. Biol. Chem. **128**: 537.
7. Jackson, G. G. & H. G. Grieble. 1957. Sulfamethoxypyridazine: pharmacological observations and clinical use in the treatment of urinary tract infections. Ann. N. Y. Acad. Sci. **69**(3): 493.

Discussion

Jay P. Sanford (*Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.*): Observations on the clinical effectiveness of chemotherapeutic agents must be interpreted with considerable caution. Knowledge of the specific etiologic agent, the natural history of infection resulting from the particular etiologic agent, and the associated presence of predisposing factors that render chemotherapy of secondary importance is essential before enthusiasm as to the effectiveness of an agent is warranted. The papers by Leming and Flanigan, Michael, and Finegold and his co-workers all take various aspects of these difficulties into consideration. Leming has clearly pointed out the necessity for antibiotic sensitivity determinations under a variety of circumstances. One specific point noted by him that warrants re-emphasis is the fact that physicians in private practice in the community obtained better results with penicillin therapy for staphylococcal infections than were observed in hospitals. This is a fairly uniform observation about the country. Although penicillin-resistant staphylococci predominate within the hospital environments, the majority of staphylococci isolated from patients who have had no contact with a hospital environment are still sensitive to penicillin. There is little to add to the interesting papers by Michael and by Finegold.

MADRIBON IN THE TREATMENT OF PNEUMONIA: A PRELIMINARY REPORT

William J. Grace
St. Vincent's Hospital, New York, N. Y.

Madribon has been used in the treatment of more than 20 patients with bronchopneumonia. All the patients were adults and were hospitalized. After appropriate laboratory tests, Madribon was given in a dose of 1.0 gm., and followed by 0.5 gm. daily for 7 to 10 days. The clinical course of the patients was closely followed with repeated physical examinations, chest X rays, blood counts, and urinalyses. Signs of dermatological manifestations of drug toxicity were carefully searched for. Sputum cultures were made on all patients, and the organisms were tested for sensitivity to the usual antibiotics. In addition, the patients received the usual symptomatic care for pneumonia, including bed rest, sedation, and expectorants where indicated. No patients in this group were considered to be critically ill.

With the exception of 2 patients with staphylococcus pneumonia (due to staphylococcus phage Type 80-81) and 2 with tuberculosis pneumonia, all recovered promptly.

Temperatures returned to normal by the third and fifth hospital days. Follow-up X rays showed complete resolution of the pneumonia. Clinical improvement and defervescence of symptoms were equally prompt, and no manifestation of drug toxicity was noted by blood count, urinalysis, or by examination of the skin.

The responses of these patients compare favorably with those of patients treated with penicillin, tetracycline, or both.

LINGUAL TONSILLITIS

J. C. Elia
Washoe Medical Center and St. Mary's Hospital, Reno, Nev.

Lingual tonsillitis, a definite clinical entity, is often overlooked in a routine examination despite the fact that its detection requires merely a laryngeal mirror. However, the problem is one that does not lie in the domain of the otolaryngologist alone. Irrespective of their specialties, all physicians might well be on the alert for disease in the area of the lingual tonsil, for it is this structure and its general location that often constitutes the key to diagnosis of many ailments frequently attributed to other causes.

The lingual tonsil is a collection of lymphoid particles behind the foramen cecum on the dorsal posterior surface of the tongue. It may be affected by acute or chronic disease in a similar way as lymphoid tissue in the palatine fossae or other parts of Waldeyer's ring. There is no fixed pattern of the lymphoid tissue in this location; it may be noted only as a small confluent swelling in the center or, in some patients, as a unilateral mass either to the right or left of the midline. Still another possibility is its appearance as two distinct masses separated by a midline groove in which the epiglottis appears to fit.

Diseases that generally involve the lingual tonsil area include: acute and chronic lingual tonsillitis, benign hypertrophy of the lingual tonsil, malignancy and abscess formation of the tonsil, aberrant lingual thyroiditis, epiglottiditis, irritation by foreign bodies, and proximal thyroglossal cyst, or duct disease with involvement of the foramen cecum.

In view of the importance of lingual tonsillitis as a possible forerunner of other disorders, it seemed desirable to review 43 cases from our experience.

Patient Material

Among the most frequent of these conditions was acute lingual tonsillitis in 27 patients (62.8 per cent), benign hypertrophy in 7 (16.3 per cent), chronic lingual tonsillitis in 5 (11.6 per cent), abscess in 3 (7 per cent), and a foreign body in 1 (2.3 per cent). These diagnostic categories and the associated symptoms in each group are shown in TABLE 1.

The symptoms of lingual tonsillitis are not constant either in type or severity. Careful examination and evaluation of the patient are necessary for a correct diagnosis. The symptoms, in the order of frequency observed in the current study, are shown in TABLE 2. In some patients more than one of these symptoms occurred simultaneously.

As in palatine tonsillitis, the diagnosis in acute lingual tonsillitis is not entirely dependent upon the size of the tonsil, but rather on the virulence of the infection that has invaded the tissue.

In benign hypertrophy the lymphoid masses were generally of equal size on either side of the midline and sufficiently large to displace the epiglottis. In two patients the tonsillar tissue actually made contact with the posterior pharyngeal wall. Both these patients were extremely allergic, and symptoms were

reported aggravated during the height of the hay fever season. This complication made it difficult to determine the cause of the cough; it might have been due to the existing allergy phenomenon or to pharyngitis resulting from contact of the lingual tonsil with the pharyngeal mucosa, or to both. The patient with the condition caused by a foreign body had lingual tonsil inflammation due to a tiny spicule of fishbone lodged in this tissue.

TABLE 1
DIAGNOSTIC CATEGORIES AND ASSOCIATED SYMPTOMS

Diagnosis	No. patients	Percentages	Symptoms										Previous tonsil or adenoid surgery	
			Otalgia	Dysphagia	Globus	Hoarseness	Loss of taste	Tickling cough	Halitosis	Dyspnea	Tongue pain	Fever	Yes	No
Acute lingual tonsillitis	27	62.8	13	17	10	7	4	16	1	3	2	7	19	8
Benign hypertrophy	7	16.3	1	6	2	0	0	3	0	0	0	0	2	1
Chronic lingual tonsillitis	5	11.6	1	1	1	1	1	1	1	0	0	0	3	2
Abscess	3	7.0	3	3	1	0	0	1	1	0	2	1	2	1
Foreign body	1	2.3	1	0	0	0	0	0	1	0	1	0	1	0
Total	43	100	19	27	14	8	5	21	4	3	5	8	30	13
Percentages			44	63	32.5	18.6	12	49	9	7	12	19		

TABLE 2
SYMPTOMS OF LINGUAL TONSILLITIS

	No. of patients	Percent
Dysphagia	27	63
Tickling cough	21	49
Otalgia (referred)	19	44
Globus	14	32.5
Fever	8	19
Hoarseness	8	18.6
Taste loss or disturbance	5	12
Halitosis	4	9
Tongue pain	5	12
Dyspnea	3	7

The series consisted of 18 males and 25 females. The females were predominantly in the age range of 16 to 35, the youngest in the group having a history of previous tonsil surgery. The males predominated in the age group from 35 to 50. The composition by age and sex is shown in TABLE 3.

Seventy per cent of these patients had previous tonsil and/or adenoid surgery.

Treatment

The treatment varies with the specific condition.

Abscess of lingual tonsil. Abscesses should be incised and drained. This

should be done preferably under general anesthesia, with endotracheal tube in place to prevent aspiration of purulent material, to make possible the probing of the abscessed cavity for the presence of a foreign body or neoplasm. If necessary, biopsy should be done at the same time.

The three cases reported were so treated, after which they were given sulfadimethoxine (Madribon*), a new low-dosage, long-acting sulfonamide that proved to be a most effective antimicrobial agent in a previous study.[1] The patients received 2 tablets (1 gm.) daily for 2 days, followed by 1 tablet daily for an additional 8 days. All 3 patients were symptomfree by the fourth day, with relief of ear pain and normal swallowing function restored. (Referred otalgia is the predominant symptom, with deep-seated involvement of the base of the tongue due to glossopharyngeal innervation of the area.)

Acute lingual tonsillitis. This condition is best treated with analgesics in addition to Madribon; all but 3 of the patients in this series were thus treated. The 3 patients who did not receive the drug were given alternate therapy because of a history of allergy or untoward drug reaction to previous sulfonamide

Table 3
Distribution According to Age and Sex

Age	Female	Male
16–20	7	0
21–25	7	1
26–30	4	1
31–35	4	2
36–40	3	4
41–45	0	9
46–50	0	1
Total	25	18

therapy. The remaining 23 patients responded well, were relieved of the acute symptoms within 3 days, and were symptom-free by the seventh day. One of the patients not treated with Madribon was given X-ray therapy because her allergy extended to antibiotics as well as sulfonamides. Within 10 days after a single treatment by irradiation she was symptom-free. Only the base of the tongue was irradiated, other parts being protected by careful shielding.

Benign hypertrophy. Hypertrophy of lingual tissue is undoubtedly best treated by irradiation at the hands of a careful roentgenologist. The quantity of this embryonic tissue may easily be reduced and symptoms relieved in a short time. Since there is no infection involved in these instances, chemotherapy is not indicated, nor is surgery, unless solitary masses that can be removed easily with ring punches or curettes are noted.

Electrocoagulation is not advised owing to the danger of malignancies developing in the scarred areas in the region of electrocoagulation. This hazard is analogous to that existing in burn scars, in which cancer sometimes develops. The practice of painting with various medications is also undesirable; the mac-

* Hoffmann-La Roche.

eration or even rubbing of an already inflamed surface with a chemical is not unlike pouring salt on a wound.

The patient with an inflammatory reaction due to the foreign body was treated chemotherapeutically for three days. After the inflammatory reaction was largely reduced, the foreign body was easily visualized, protruding from the base of the tongue. The mass was removed and chemotherapy continued, resulting in complete disappearance of the symptoms.

The response of the patients with chronic lingual tonsillitis to the medication was extremely good.

Discussion

A review of the above cases raises the question of the part that surgery should play in the treatment of infections involving the tonsils and adenoids. More than two-thirds of the patients in our study had a previous tonsil operation and/or adenoid surgery. In some of these the enlargement is a compensatory hypertrophy, that is, a physiological response to the need for additional protective lymphoid tissue. A good deal of tonsil and adenoid surgery must be evaluated with this in mind. When tonsils and adenoids are removed unnecessarily or without adequate indications, compensatory hypertrophy of the lingual lymphoid masses will result.

A history of frequent colds and sore throat alone do not constitute sufficient justification for adenotonsillectomy or tonsillectomy. Primary tonsillitis is a justified cause for removal, but a tonsillitis or adenoiditis that *follows* an upper respiratory infection is not adequate indication for removal of this tissue.

First and foremost, the infection must be controlled. For this purpose my own preference is for chemotherapy rather than antibiotic treatment, for reasons of efficiency, safety, convenience, and cost of therapy.

Infections encountered in ear, nose, and throat (ENT) practice respond very well to sulfonamide therapy. (Except for the acid-fast organisms and spirochetes, the causative agents are those that are also controlled by penicillin and streptomycin.) A review of the history of sulfonamides reveals the dramatic disappearance of mastoiditis with the introduction of chemotherapy. Second to efficiency, the major asset of sulfonamides, safety, is a paramount characteristic. Irreversible deafness and dizziness associated with streptomycin and neomycin[2, 3] and skin and other reactions with both penicillin[4-6] and streptomycin are sufficient reason for employing these antibiotics only as a last resort in ENT work. Superinfection, a major worry with all antibiotics, is a negligible hazard with sulfonamides.

The convenience of a single daily dose of sulfadimethoxine is a special consideration in patients who have difficulty in swallowing or are nauseated and/or vomiting, as it is in the ambulatory patient. Cost of the treatment is an aspect that must not be overlooked. Often it is a factor that will determine whether or not the patient receives medication at all. A patient may neglect treatment because he feels he cannot afford the cost of the drug. The cost of sulfadimethoxine is approximately one third that of the average antibiotic. Taking into account the fact that it is administered only once daily, as against 4 times daily for most antibiotics, the economy factor in sulfadimethoxine therapy is therefore about as 1 to 10 compared with antibiotics.

The family physician or pediatrician is actually in a much better position to evaluate the need for tonsil and adenoid surgery than the specialist to whom a case is referred for such an evaluation. If the physician has followed a patient for an adequate period and has a genuine interest in his well-being, he will be in a most advantageous position to advise tonsil surgery or, if he has adequate experience he may even perform it himself. A specialist who sees a patient for the first time is in no better a position than the corner druggist to advise or recommend surgery of this type unless the indications are so glaring that even a layman can tell. Unfortunately, many cases of tonsillectomy benefit the surgeon more than the patient.

The three indications for adenotonsillectomy include the following:

(1) Repeated attacks of primary tonsillitis, and/or adenoiditis with or without frequent colds or ear infections that follow (not precede) the attack of lymphoid inflammation.

(2) The appearance of the adenoid facies, snoring, and difficulty in swallowing or breathing due to the size of the lymphoid masses.

(3) Frequent attacks of tonsillitis with cervical adenitis that does not disappear after the lymphoid infection seems to subside.

The presence of symptomless enlargement of the tonsils is no indication for surgical removal, which does not enhance the patient's health, but rather jeopardizes it. It is in many of these patients that compensatory lingual lymphoid enlargement occurs.

Summary and Conclusions

Lingual tonsillitis as a clinical entity is reviewed and the symptomatology and treatment of 43 patients seen in private practice are described. More than 60 per cent of these cases were acute, and nearly 12 per cent chronic.

With the exception of three patients who were allergic to sulfonamides, all were treated with Madribon with excellent results.

In patients with abscesses of the lingual lymphoid tissue the area was incised and drained. Adjunctive therapy with Madribon proved highly successful.

Attention is once more drawn to the fact that this tissue at the base of the tongue is a most fertile source of trouble both in acute and chronic diseases and infections.

In evaluating these patients from the standpoint of infection, one must not lose sight of the fact that malignancy may also develop.

References

1. Elia, J. C. 1959. Preliminary report on a new antimicrobial agent, sulfadimethoxine (Madribon) in the treatment of respiratory and chronic ear infections. Antibiotic Med. & Clin. Therapy. **6** (Suppl. 1) : 61.
2. Greenwood, G. J. 1959. Neomycin ototoxicity. A.M.A. Arch. Otolaryngol. **69:** 390.
3. Naunton, R. F. & P. H. Ward. 1959. The ototoxicity of Kanamycin sulfate in the presence of comprised renal function. A.M.A. Arch. Otolaryngol. **69:** 398.
4. Lowell, F. C. 1955. Allergic reactions to antibiotics. Modern Med. **23:** 91.
5. Welch, H. 1958. Fifth annual symposium on antibiotics, Oct. 2–4, 1957, Washington, D. C. Antibiotics Ann. 1957–1958. : 1.
6. Zimmerman, M. C. 1959. Chronic penicillin urticaria from dairy products, proved by penicillinase cures. A.M.A. Arch. Dermatol. **79:** 1.

SOME CLINICAL EXPERIENCES WITH A NEW LOW-DOSAGE SULFONAMIDE, SULFADIMETHOXINE, CHIEFLY IN RESPIRATORY TRACT INFECTIONS

L. E. Skinner
Lakewood Clinic, Tacoma, Wash.

As a general practitioner of medicine and not an experimental scientist, my approach to the problem of the treatment of any disease is pragmatic and not that of the test tube or the experimental animal. In the course of treating an average of thirty patients daily, my question is "Does it work?"

Recently, a young mother brought her two-year-old child to the office for an examination. The child had fever, enlarged and infected tonsils, and a cough. Before I was able to write a prescription, she produced an empty bottle, and said:

"I want some more of this medicine. You prescribed it for my other girl, and it is the best medicine they ever had."

I looked up the chart, and found that several months before I had given her a suspension of sulfadimethoxine (Madribon*), so I wrote another similar prescription. Hardly a day goes by without a phone call or a request from a patient for "some more of that new medicine for colds."

I had another patient who came in with a cold. This time as I was getting ready to write a prescription, he said, "Look, Doc, go easy on my pocketbook this time. The last prescription cost me fifteen dollars." So I wrote a prescription for him for Madribon, which is much cheaper, and it helped his cold.

My first experience with sulfadimethoxine was during the summer of 1958. It has been reported[1-4] that this new antibacterial was especially effective in low dosage in many types of infections, chiefly of the respiratory tract. Because of the many new preparations introduced on the market, I confess that I was highly skeptical but, since toxicity did not seem to be a factor,[5, 6] I decided to try it. The first few patients were so enthusiastic about it that I decided to give the drug a systematic trial.

Since that time I have used it in over 200 patients, about 90 per cent of them with infections of the respiratory tract or with consequent complications. Of this total number, I have been able to obtain follow-up data on about 160.

I have used several dosage schedules. The commonest one is an initial dose of 1 gm., with a maintenance dose of 0.5 gm. once daily. In many cases I gave the same initial dose, but with a maintenance dose of 0.5 gm. twice daily. About a dozen patients received an initial dose of 2 gm., with a maintenance dose of 0.5 gm. daily. I was interested to learn whether their infections would respond any faster or if they would develop any nausea or other side effects. In none of these patients was it necessary to suspend medication because of side effects, but since the response did not seem to be any faster than with the standard dosage, the larger doses were discontinued. Since then I have routinely used the first-mentioned dosage schedule, except in cases in which I felt that the patient's illness justified the larger maintenance doses. If this

* Hoffmann-La Roche.

procedure does not appear to be entirely rational, it is important in acutely ill patients who feel they are not getting enough medicine on a single 0.5-gm. tablet daily.

The two youngest patients in my series were brothers, aged 4 and 16 months, both of whom had severe colds complicated by bronchopneumonia. Both were treated with a suspension of Madribon, and both responded promptly to these dosages. The dose used was dr. ii for the younger, and dr. iv for the older, initially, then half that dosage twice daily for 2 days, then single daily doses of dr. i and dr. ii, respectively.

In some types of illnesses Madribon is used as adjunct therapy. My customary treatment of otitis media has been to give 3 injections of penicillin, and concurrently the sulfa, continuing the oral medication for a week or 10 days after withdrawing the penicillin. In the treatment of 18 cases in this series, all 18 patients responded promptly and completely to this therapy. In a few cases of tonsillitis the treatment was initiated with a single injection of 600,000 U. of penicillin or 300 mg. of chloromycetin, and then followed by Madribon.

In most cases of simple respiratory tract infections, Madribon alone was used, the dosage schedule being 1 tablet daily after the initial dose, and treatment continued for about 7 to 10 days.

Because of the good results obtained with the upper respiratory infections, I tried this new drug on other infections. Consequently, although this paper deals chiefly with infections of the respiratory tract, I shall cite one case of a patient having an infection of another type.

A 35-year-old woman who had severe psoriasis, complicated with multiple furunculosis, chiefly of the axillae, the vulva, and perineum, had been treated with antibiotics, vaccine, hot packs, and daily incision of the new furuncules. In desperation I started large doses of sulfadimethoxine. It was necessary to open a few more furuncles, but within a week no new ones were forming, and soon she became free of them, although the psoriasis continued unchanged. Since then she has taken the usual dose of Madribon at intervals and has been almost entirely free of recurrences.

Not all treatments have been successful. An infected olecranon bursa failed to respond, and an infected wound of the knee also failed to be affected by Madribon; both cases required surgical intervention.

My results may best be summarized by a few statistics: out of a total of over 200 patients treated with Madribon, follow-up records were obtained in 162, divided as follows (TABLE 1): common cold, 66; sore throat, 22; bronchitis, 19; otitis media, 18; tonsillitis, 13; pneumonia and bronchopneumonia, 8; furunculosis, 1; and in the miscellaneous group, 15. The over-all results were as follows: good to excellent, 139 cases (86 per cent); fair, 17 cases (10.5 per cent); poor, 6 cases (3.7 per cent).

As already mentioned, no complications from using the drug were encountered, and in no case was it necessary to discontinue the medication because of side effects.

Routine cultures were not taken because I was more interested in clinical results than in determining the response to specific organisms. However,

cultures were taken in 11 cases, and the reports showed *Staphylococcus aureus* in 3 cases; β-hemolytic *Streptococcus* in 4 cases; hemolytic *Staphylococcus* in 1 case, and *Neisseria catarrhalis* in 1 case.

Repeat cultures in two of the cases of β-hemolytic *Streptococcus* showed normal flora.

Based on our experience, several points are worthy of mention. I found that the dosage should be adjusted both to the individual and his disease. The treatment of disease is not merely a matter of mathematical calculations based on so many milligrams per kilogram of body weight.

Often we find that the patient refuses to take the medication prescribed. We found no instances of this while using Madribon, either in the suspension or tablet form. I think that the relative infrequency of the dose was a definite factor in this.

Table 1
Summary of Clinical Results with Madribon

Conditions treated	Number of patients
Undifferentiated respiratory infection (common cold)	66
Bronchitis	19
Otitis media	18
Tonsillitis	13
Sore throat	22
Pneumonia (bronchial)	8
Multiple furunculosis	1
Miscellaneous infections	15
Total	162

Results: Good to excellent, 85.8%; fair to poor, 10.5%; poor, 3.7%.

I repeatedly heard patients or their parents express gratitude for the relative inexpensiveness of the prescription. The average cost of treatment was not much over 25 cents per day.

In summary, then, it can be said that a new antibacterial, sulfadimethoxine, was tried on over 200 patients, chiefly in the treatment of respiratory tract infections. Among these infections were the common cold, bronchitis, otitis media, tonsillitis, sore throat, and pneumonia. Cultures in a limited number of patients showed various pathogens, including *Staphylococcus aureus* and hemolytic *Staphylococcus*, β-hemolytic *Streptococcus*, and *Neisseria catarrhalis*. Good to excellent results were obtained in 86 per cent of the cases, fair results in 10.5 per cent, and poor results in 3.7 per cent of a total of 162 patients on whom a follow-up was made.

In no cases were complications due to the use of the drug encountered, and in no case was it necessary to withdraw the medication.

Acceptance of the drug by patients was excellent, and no cases were reported in which the patient, whether adult or child, refused to take the prescribed medication.

Finally, the cost of the preparation is considerably less than the cost of the usually recommended doses of available broad-spectrum antibiotics.

References

1. Leming, B. H., Jr., C. Flanigan, Jr., B. R. Jennings. 1959. Clinical evaluation of sulfadimethoxine (Madribon), a wide-spectrum antibacterial. Antibiotic Med. & Clin. Therapy. **6** (Suppl 1). : 32.
2. Michael, T. D. 1959. Clinical trial with a new antimicrobial agent, sulfadimethoxine (Madribon), in common respiratory infections. Antibiotic Med. & Clin. Therapy. (Suppl. 1). **6**: 57.
3. Townsend,, E. H. Jr. & A. Borgstedt. 1959. Preliminary report of clinical experience with sulfadimethoxine, a new long-acting sulfonamide. Antibiotics Ann. 1958–1959. : 64.
4. Elia, J. C. 1959. Preliminary report on a new antimicrobial agent, sulfadimethoxine (Madribon) in the treatment of respiratory and chronic ear infections. Antibiotic Med. & Clin. Therapy. **6** (Suppl. 1) : 61.
5. Boger, W. P. 1959. A new long-acting antibacterial sulfonamide, 2,4-dimethoxy-6-sulfanilamido-1,3-diazine. A comparative study. Antibiotics Ann. 1958–1959. : 48.
6. Leff, W. A. 1959. A clinical study with sulfadimethoxine (Madribon) in cystitis associated with paraplegia. Antibiotic Med. & Clin. Therapy. **6** (Suppl. 1) : 44.

Discussion

Jay P. Sanford (*Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.*): As emphasized in discussion of several earlier papers, knowledge of specific etiological agents and the natural history of an infection are essential for the critical evaluation of the effectiveness of chemotherapeutic agents. Dingle and his co-workers[1] observed 61 families for 3 years, utilizing repeated clinicomicrobiological studies, and found that 95 per cent of common respiratory disease could not be diagnosed by extensive bacteriological or virological techniques. Only 2.5 per cent of 4428 illnesses were associated with organisms that might be expected to respond to antibiotics or sulfonamides. Furthermore, controlled studies on the efficacy of antibiotic or sulfonamide therapy in the treatment of uncomplicated respiratory infections in children have been reported by Hardy and Traisman.[2] In 217 patients divided into approximately 4 equal groups, they noted that the complication rate ranged from 13.0 to 17.6 per cent, with no significant differences between treated and untreated groups. They observed that complications were more apt to develop in children less than 4 years of age, who were seen during the winter months, who had leukocyte counts in excess of 10,000 per cubic millimeter, and who had β-hemolytic streptococci in their throats. They reported that antibiotics decreased the complication rate under these circumstances, but actually increased the complication rate in patients with leukocyte counts of less than 10,000 per cubic millimeter. When considering observations such as these, it would seem extremely difficult to evaluate the effectiveness of sulfadimethoxine in the management of clinical upper respiratory tract infections.

References

1. Dingle, J. H., G. F. Badger, A. E. Feller, R. G. Hodges, W. S. Jordan, Jr. & C. H. Rammelkamp, Jr. 1953. A study of illness in a group of Cleveland families. I. Plan of study and general observations. Am. J. Hyg. **58**: 16.
2. Hardy, L. M. & H. S. Traisman. 1956. Antibiotics and chemotherapeutic agents in the treatment of uncomplicated respiratory infections in children. J. Pediat. **48**: 146.

THE TREATMENT OF RESPIRATORY, URINARY TRACT, AND SOFT-TISSUE INFECTIONS WITH MADRIBON

George A. Moore
Worcester, Mass.

We are keenly interested in new therapeutic agents that will assist us in the control and cure of diseases of infectious origin, particularly since the advent of the resistance of certain organisms to many antibiotics.

When Madribon in its current oral form was investigated at the Worcester State Hospital, it became evident that this drug had a good potential.

Structurally a sulfonamide, but clinically in a class by itself, Madribon exerts a high degree of effectiveness against a wide range of pathogens. It was shown clinically that effective blood levels are maintained for a full 24 hours with a single dose of Madribon tablets and that therapeutic action could be obtained with just 1 daily dose; it was equally effective when given in divided doses. Madribon represents a genuine advance in the treatment of bacterial infections. Its wide spectrum, high clinical effectiveness, exceptionally low incidence of side effects, and flexibility of dosage warrant its use in treating infections due to antibiotic-resistant strains such as staphylococci, *Pseudomonas*, *Proteus*, and *Escherichia coli*. Madribon was more than 95 per cent effective in the treatment of respiratory, urinary tract, and soft-tissue infections.

Clinical Study

In my clinical study of 50 cases I used dosages ranging from 0.25 gm. every 12 hours to 1 gm. every 24 hours, depending on the patient and type of bacterial infection. Certain patients had multiple infections. TABLE 1 summarizes the results. It is noteworthy that only 2 cases of drug intolerance or allergy were encountered. TABLE 2 gives the distribution of the 50 cases according to infection.

Three patients had prostatitis, chronic in nature, which had been recurrent for several years. After Madribon therapy for 21 days these patients were symptom-free, and the prostatitic secretions were free of pathogenic bacteria.

Six patients with cases of diagnosed acute prostatitis were free of symptoms and of pathogenic bacteria in their prostatic organs after 10 days' therapy with Madribon. Two patients had recurrence of symptoms after 1 week's therapy with the drug; these symptoms recurred 1 month after therapy.

All 7 urethritis cases responded well to the therapy.

Nine pneumonia cases recovered completely and were clear on X-ray examination after 1 week's therapy with Madribon.

Eleven pharyngitis cases responded very well and were symptom-free after 4 days' therapy on Madribon, while 2 cases developed side reactions of urticaria.

Six abscess cases recovered completely on varied doses of Madribon, and 2 wound infection cases did equally well.

Two patients with pyelonephritis were treated and recovered completely after 1 week of therapy.

TABLE 1

No.	Name	Disease	Results				
			Dose*	Good	Fair	Poor	Remarks
1	A.B.	Prostatitis, chronic	3	X			
2	D.L.	Prostatitis, chronic	3	X			
3	C.P.	Prostatitis, chronic	3	X			
4	M.M.	Prostatitis, acute	4	X			
5	M.W.	Prostatitis, acute	4	X			
6	L.D.	Prostatitis, acute	4	X			
7	C.D.	Prostatitis, acute	4	X			
8	R.E.	Prostatitis, acute	4	X			
9	J.D.	Prostatitis, acute	4	X			
10	H.L.	Prostatitis, acute	2			X	Recurrence
11	H.B.	Prostatitis, acute	2			X	Recurrence
12	N.P.	Urethritis, acute	2	X			
13	D.M.	Urethritis, acute	2	X			
14	J.B.	Urethritis, acute	2	X			
15	L.B.	Urethritis, acute	4	X			
16	J.L.	Urethritis, acute	4	X			
17	M.E.	Urethritis, acute	4	X			
18	C.M.	Urethritis, acute	4	X			
19	S.L.	Pneumonia	4	X			
20	G.A.	Pneumonia	4	X			
21	A.A.	Pneumonia	2	X			
22	J.J.	Pneumonia	2	X			
23	R.S.	Pneumonia	2	X			
24	C.H.	Pneumonia	2	X			
25	M.H.	Pneumonia	2	X			
26	D.M.	Pneumonia	3	X			
27	T.E.	Pneumonia	3	X			
28	J.E.	Pharyngitis, acute	1			X	Urticaria
29	B.B.	Pharyngitis, acute	1			X	Urticaria
30	E.F.	Pharyngitis, acute	1	X			
31	J.C.	Pharyngitis, acute	2	X			
32	S.V.	Pharyngitis, acute	2	X			
33	H.B.	Pharyngitis, acute	2	X			
34	L.T.	Pharyngitis, acute	3	X			
35	J.W.	Pharyngitis, acute	3	X			
36	L.L.	Pharyngitis, acute	4	X			
37	E.Z.	Pharyngitis, acute	4	X			
38	A.S.	Pharyngitis, acute	4	X			
39	J.S.	Pharyngitis, acute	2	X			
40	F.F.	Pharyngitis, acute	2	X			
41	G.G.	Abscess, acute	2	X			
42	C.G.	Abscess, acute	2	X			
43	R.B.	Abscess, acute	2	X			
44	J.M.	Abscess, acute	2	X			
45	E.H.	Abscess, acute	2	X			
46	R.S.	Abscess, acute	3	X			
47	J.G.	Wound infection, acute	4	X			
48	M.S.	Wound infection, acute	4	X			
49	J.L.	Pyelonephritis, acute	3	X			
50	C.B.	Pyelonephritis, acute	3	X			

* 1 indicates a dose of 0.50 gm. every 12 hours; 2, 0.50 gm. every 24 hours; 3, 1 gm. every 12 hours; and 4, 1 gm. every 24 hours.

TABLE 2

Disease	No. of cases
Prostatitis, chronic	3
Prostatitis, acute	8
Urethritis	7
Pneumonia	9
Pharyngitis	13
Abscesses	6
Wound infections	2
Pyelonephritis	2
	50

Summary

A clinical evaluation of Madribon was carried out on 50 patients with no histories of sulfonamide allergy or intolerance. Several cases were reviewed and the most noteworthy observation was that of the desired response of these patients within only a few days after administration of the drug.

There were 2 instances in which sulfonamide intolerance was experienced. Forty-eight of the 50 patients recovered completely and drug therapy was discontinued on the 2 patients who showed intolerance.

As a result of observations made in the administration of Madribon, it is felt that this drug parallels that of many of the antibiotics. It has been shown to be clinically effective against many antibiotic resistant organisms, and provides more economical therapy and the convenience of flexibility of dosage.

The usual precautions in sulfonamide therapy should be observed, including the maintenance of an adequate fluid intake; this is a salient point in sulfonamide therapy.

Although the above points should be kept in mind, Madribon is an outstanding drug and merits consideration by the practicing physician in the treatment of bacterial infections.

Acknowledgment

The Madribon used was made available by the Department of Clinical Research, Hoffmann-La Roche Inc., Nutley, N. J.

MODERN SULFONAMIDES IN PEDIATRIC PRACTICE

C. W. Daeschner

Department of Pediatrics, Baylor University College of Medicine, Houston, Tex.

The place of sulfonamide medications in the chemotherapy of bacterial infections has been firmly established for many years, and little new has been added in the past decade. Conversely, the development of new sulfonamide compounds with improved pharmacological properties has been a consistently active field of chemistry and medicine; new preparations have appeared almost yearly. The recent development of long-acting sulfonamides such as sulfadimethoxine, which are therapeutically effective and low in toxicity, characterizes what might be called a modern era of sulfonamide therapy. For physicians who treat infants and children, the availability of a once-a-day oral antibacterial medication has been particularly helpful.

The purpose of the present studies was to examine the absorption, distribution, excretion, toxicity, and general therapeutic effectiveness of sulfadimethoxine in infants and children.

Material and Methods

Sulfonamide levels in blood, plasma, and urine were determined by the standard Bratton-Marshall technique on 0.1-ml. samples of blood or serum and from 1- to 5-ml. aliquots of urine. Total sulfonamide in urine was determined following hydrolysis with heat and acid. All medication was given orally. Both tablet (0.5 gm.) and microcrystalline suspension (10 per cent) forms of sulfadimethoxine were studied. A control or "zero" blood specimen was obtained in all absorption studies and a control urine in all excretion studies. The penetration of sulfadimethoxine into the cerebrospinal or subdural fluid was evaluated in patients who had some therapeutic or diagnostic indication for puncture. No patient was subjected to puncture for the primary purpose of determining sulfonamide level. Following the suggestions of Boger, plasma or serum levels were used in the penetration studies, rather than whole blood levels as in the absorption studies.

Body surface area as a basis for the estimation of sulfonamide dose in infants and children has been utilized in these studies to standardize blood concentrations and to avoid the necessity for developing multiple per-kilogram dose schedules. Surface area was estimated from weight alone in most instances. The use of body surface area in this manner does not constitute a more precise approach to dosage estimation for the individual patient, but rather represents a convenient manner in which subjects of widely variable size may be given a dose that will yield similar blood levels. A dose of 0.5 gm. per square meter ($m.^2$) of body surface area represents an approximate dose range of from 15 mg./kg. in the older child to 25 mg./kg. in the infant.

The patients treated with sulfadimethoxine were infants and children attending the pediatric clinic or hospitalized in the pediatric inpatient division of the Jefferson Davis City County Hospital, Houston, Texas. They ranged in age from 4 months to 14 years, in weight from 6 kg. to 40 kg., and in surface area

from 0.33 to 1.34 m.^{2} No patients under 3 months of age were included. All were treated with an initial dose of 1.0 gm./m.^{2} of body surface area, followed by 0.5 gm./m.^{2} of body surface area daily thereafter. This schedule was chosen for all patients in order to standardize the circumstances of observation and to give ample opportunity for evidence of toxicity to manifest itself. All patients were given at least 5 days of treatment; the majority received 7 to 10 days of treatment.

Since various investigators have not always agreed upon the sulfonamide level that can be considered therapeutically effective, we have arbitrarily chosen blood free sulfonamide levels in the range of 5 to 8 mg. per cent as sufficient for the effective treatment of most sulfonamide-sensitive infections.

Results

Laboratory investigations. The rate and degree of absorption of sulfadimethoxine following a single oral dose were evaluated in 33 infants and children over a 48-hour period. TABLE 1 summarizes the average values, and lists the range for each medication form and dosage level. The 0.5-gm./m.^{2} dose in suspension form produced a peak level at 3 hours, and most patients still had satisfactory levels 12 hours later. The same dose given in tablet form was similarly effective in maintaining the blood level. The administration of a 1.0- or 1.5-gm./m.^{2} dose of the suspension produced a peak level at 3 hours above 15 mg. per cent, and effective levels were still present 48 hours later. The larger dose did not produce a higher peak level, but did lead to a more sustained level. Administration of 1.0- and 1.5-gm./m.^{2} doses of sulfadimethoxine as the tablet form produced satisfactory levels 3 hours later, but peak levels were not reached until the twelfth hour. The peak levels were sustained, and averaged 8.5 mg. per cent with the 1.0-gm. dose and 11.3 mg. per cent with the 1.5-gm. dose. In these studies the suspension form appeared definitely superior to the tablet form in both degree and rapidity of absorption.

A multiple-dose schedule for sulfadimethoxine administration was selected on the basis of the single-dose schedule as 0.5 gm./m.^{2} initially, followed by 0.25 gm./m.^{2} daily. TABLE 2 lists the blood free sulfonamide levels obtained on this schedule in 18 infants and children. The tendency for certain individual subjects to reach levels below 5 mg. per cent on this schedule suggested to us that for serious infections a dose schedule twice as great would be desirable (1.0 gm./m.^{2} followed by 0.5 gm./m.^{2} daily).

The excretion of sulfadimethoxine in the urine occurs principally in the free form. TABLE 3 summarizes the free and the total sulfonamide in the urine (as percentage of dose given) per 12-hour period and on a cumulative basis. In these 4 patients an average of 80 per cent of the administered dose of sulfonamide was excreted in the urine over a 96-hour period, 57 per cent of the dose as the free form. Concentrations of free sulfonamide in the urine varied from 7 to 121 mg. per cent in the first 24 hours after administration of the single oral dose of sulfadimethoxine and from 19 to 66 mg. per cent in the second 24-hour period. On the third day the urine levels ranged from 6 to 30 mg. per cent, and on the fourth and final day of observation urinary concentrations ranged from 3 to 21 mg. per cent.

TABLE 1

SINGLE-DOSE ABSORPTION STUDIES OF SULFADIMETHOXINE IN INFANTS AND CHILDREN

Number of patients studied		Age (years)	Weight (kg.)	Surface area ($m.^2$)	Blood free sulfonamide level—mg. per cent					
					3 hours	6 hours	9 hours	12 hours	24 hours	48 hours
Subjects receiving 0.5 gm./$m.^2$ (10% suspension)										
5	Average	7	24	0.90	7.5	6.6	5.1	4.8	3.4	1.4
	Range	4 to 12	13 to 48	0.6 to 1.5	6 to 8	6 to 8	4 to 7	3 to 6	2 to 5	0 to 4
Subjects receiving 1.0 gm./$m.^2$ (10% suspension)										
5	Average	3	16	0.63	17.4	15	13.4	9.1	7.4	4.1
	Range	¼ to 8	7 to 25	0.4 to 0.8	11 to 24	9 to 19	8 to 18	5 to 12	4 to 11	2 to 8
Subjects receiving 1.5 gm./$m.^2$ (10% suspension)										
6	Average	2	10	0.45	15.9	16.1	14.8	13.2	9.6	3.8
	Range	¼ to 6	7 to 18	0.3 to 0.7	12 to 21	14 to 20	9 to 18	12 to 14	8 to 11	2 to 5
Subjects receiving 0.5 gm./$m.^2$ (tablets)										
6	Average	7	22	0.86	—	7.7	—	6.0	4.0	—
	Range	2½ to 10	14 to 32	0.6 to 1.1	—	5 to 11	—	5 to 7	2 to 6	—
Subjects receiving 1.0 gm./$m.^2$ (tablets)										
5	Average	6	19	0.77	5.8	7.8	7.9	8.5	6.0	2.1
	Range	1 to 13	9 to 31	0.4 to 1.1	2 to 9	6 to 10	6 to 13	6 to 13	4 to 9	0.8 to 4
Subjects receiving 1.5 gm./$m.^2$ (tablets)										
6	Average	7	20	0.80	5.9	8.2	9.4	11.3	6.7	3.7
	Range	2 to 9	10 to 26	0.5 to 1.0	4 to 11	6 to 15	4 to 13	3 to 18	3 to 11	1 to 6

Table 4 shows the penetration of sulfadimethoxine into the cerebrospinal or subdural fluid in 14 infants and children as compared to the plasma free sulfonamide level. The degree of pleocytosis and the protein are listed to indicate the extent of meningeal inflammation present. Since no parenteral

Table 2

Multiple-Dose Absorption Studies of Sulfadimethoxine in Infants and Children Receiving an Initial Oral Dose of 0.5 gm./m.² Followed by 0.25 gm./m.² Daily

Number of patients studied		Age (years)	Weight (kg.)	Surface area (m.²)	Blood free sulfonamide level—mg.%							
					6 hrs.	12 hrs.	24 hrs.*	30 hrs.	48 hrs.*	54 hrs.	72 hrs.*	78 hrs.
Subjects receiving 10% suspension dosage form.												
12	Average	5.6	19	0.80	7.7	6.2	4.8	8.1	4.4	7.5	4.6	7.7
	Range	3 to 10	12 to 31	0.6 to 1.2	6 to 12	4 to 10	3 to 7	5 to 14	3 to 11	6 to 10	3 to 7	6 to 11
Subjects receiving tablet form of medication												
6	Average	7	22	0.86	7.7	6.0	4.0	5.7	3.7	5.5	3.6	6.3
	Range	2½ to 10	14 to 32	0.6 to 1.1	5 to 11	5 to 7	2 to 6	4 to 10	2 to 7	3 to 12	1 to 9	4 to 12

* Dose following this blood specimen.

Table 3

The Urinary Excretion of Free and Total Sulfonamide in 4 Children Following a Single Oral Dose of 1.0 gm. of Sulfadimethoxine (Tablets)

Patient No.	Period (with urinary excretion expressed as percentage of dose given)															
	0 to 12 hours		12 to 24 hours		24 to 36 hours		36 to 48 hours		48 to 60 hours		60 to 72 hours		72 to 84 hours		84 to 96 hours	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
1	2	2	10	14	26	46	11	13	7	9	3	4	2	2	1	4
2	10	12	16	20	16	23	10	10	5	8	8	8	5	16	1	5
3	2	15	15	20	17	25	10	12	6	7	4	5	—	—	2	2
4	9	11	11	15	9	13	10	12	9	13	3	4	3	3	2	2
Average for period	13		17		17	27	10	12	7	9	5	5	3	7	2	3
Average cumulative excretion: Free					30		40		47		52		55		57	
total						44		56		65		70		77		80

form of sulfadimethoxine was available at the time of these studies, all doses are of the oral form.

Clinical studies. Studies to determine the acceptability and the incidence of toxic reactions to sulfadimethoxine were carried out in 590 consecutive infants and children. The majority of treatments were carried out on an outpatient basis.

Table 5 lists the diagnosis, duration of therapy, and clinical response in 399 infants and children who received sulfadimethoxine as the sole antibacterial agent. To facilitate the evaluation of the therapeutic response, subjects

TABLE 4

PENETRATION OF SULFADIMETHOXINE INTO THE CEREBROSPINAL FLUID AS THE FREE SULFONAMIDE AS COMPARED TO THE PLASMA FREE SULFONAMIDE LEVEL IN 14 INFANTS AND CHILDREN

Patient	Diagnosis	Wt. (kg.)	Dose mg./kg.	Body fluid examined			Duration of therapy	Free sulfonamide—mg. %		
				Source	Cells	Protein		Plasma	Fluid	%
M.P.	*Cryptococcus* meningitis	12.0	25	CSF	0	16 mg.%	1½ hrs.	25.7	0	0
C.G.	Febrile seizure	3.5	60	CSF	5	34 mg.%	11 hrs.	15.6	1.3	8
B.O.	Aseptic meningitis	56.0	35	CSF	84	35 mg.%	30 hrs.	16.1	1.9	12
K.W.	Aseptic meningitis	10.0	50	CSF	66	14 mg.%	36 hrs.	21.9	3.1	14
S.H.	*Hemophilus influenzae* meningitis	9.5	25	CSF	45	52 mg.%	3 days	5.6	0	0
L.D.	*H. influenzae* meningitis	10.0	30	CSF	350	84 mg.%	4 days	5.2	2.3	44
S.D.	*H. influenzae* meningitis	6.0	10	CSF	160	1 Pos. Pandy	4 days	6.2	0	0
L.B.	*Diplococcus pneumoniae* meningitis	9.0	15	subdural	0	1200 mg.%	4 days	13.1	1	8
L.B.	*D. pneumoniae* meningitis	9.0	15	subdural	0	1300 mg.%	6 days	13.5	1	8
L.B.	*D. pneumoniae* meningitis	9.0	15	subdural	0	900 mg.%	8 days	18.1	5.3	29
L.B.	*D. pneumoniae* meningitis	9.0	15	CSF	0	64 mg.%	8 days	18.1	1	5
M.B.	*H. influenzae* meningitis	6.0	20	CSF	15	Neg. Pandy	12 days	3.8	0	0
J.H.	*H. influenzae* meningitis	6.0	40	CSF	0	87 mg.%	12 days	11.6	1	9
S.D.	*H. influenzae* meningitis	6.0	10	CSF	56	Neg. Pandy	14 days	1.2	0	0

were selected from those patients in whom definite and clear-cut symptoms and signs were present. Sixty-four per cent of the patients could be classed as having a good response to therapy in that they were well at the time of the follow-up visit, while 28 per cent more were improved but not completely normal when they returned for the follow-up visit. Eight per cent of the patients

TABLE 5

THE RESPONSE OF 399 INFANTS AND CHILDREN WITH VARIOUS INFECTIONS TO SULFADIMETHOXINE ALONE GIVEN AS 1.0 GM./M.² INITIALLY, FOLLOWED BY 0.5 GM./M.² DAILY

Diagnosis	Total duration of sulfonamide therapy (days)			Response of patients to treatment with sulfadimethoxine alone		
	1 to 5	6 to 11	12+	Good	Improved	Poor
Bronchopneumonia	1	18	2	14	3	4
Lobar pneumonia	0	5	2	3	2	2
Tonsillitis, acute	1	62	3	52	10	4
Otitis media, acute	0	84	4	52	27	9
Pyoderma*	0	19	0	13	3	3
Cystitis and ? pyelonephritis	0	4	3	5	2	0
U.R.I. with fever†	5	159	0	114	42	8
Bronchitis, acute	1	26	0	2	23	2
Total	8	377	14	255	112	32
Per cent (of 399)				64%	28%	8%

* Including furunculosis, infected abrasions, and so on.
† Including pharyngitis, sinusitis, laryngotracheitis, and laryngitis.

TABLE 6

THE RESPONSE OF 146 INFANTS AND CHILDREN WITH VARIOUS INFECTIONS TO TREATMENT WITH SULFADIMETHOXINE 1.0 GM./M.² INITIALLY, FOLLOWED BY 0.5 GM./M.² DAILY, PLUS AN ANTIBIOTIC AGENT*

Diagnosis	Total duration of sulfonamide therapy (days)			Response of patients to treatment with sulfadimethoxine plus an antibiotic		
	1 to 5	6 to 11	12+	Good	Improved	Poor
Bronchopneumonia	4	33	2	18	19	2
Lobar pneumonia	0	25	0	20	4	1
Tonsillitis, acute	0	14	0	14	0	0
Otitis media, acute	0	18	0	8	7	3
Pyoderma	0	5	0	5	0	0
Cystitis and ? pyelonephritis	0	1	1	1	1	0
U.R.I. with fever	0	33	0	2	31	0
Bronchitis, acute	0	2	0	2	0	0
Meningitis: *H. influenzae*	0	0	4	2	2	0
D. pneumoniae	0	0	2	0	2	0
Undetermined	0	0	2	0	0	2
Total	4	131	11	72	66	8
Per cent (of 146)				49%	45%	6%

* The antibiotic was parenterally administered penicillin in all but 10 instances.

treated did not improve on sulfadimethoxine alone and required the addition of antibiotic agents.

A group of 146 infants and children was treated with sulfadimethoxine plus an antibiotic agent, usually parenteral penicillin (TABLE 6). No estimate of the therapeutic contribution of sulfadimethoxine in these patients can be reached.

TABLE 7 lists the observed complications encountered in the course of administration of sulfadimethoxine to the total group of 590 infants and children. Although 16 patients vomited during the period of treatment, only 3 did so repeatedly. Since vomiting is a common accompaniment of many childhood illnesses, this over-all incidence of 2.7 per cent is considered to be exceptionally low. Some skin reaction was exhibited in 1.1 per cent of the patients. Two were urticarial and lasted only 1 day, while 5 were morbilliform and lasted from 1 to 3 days. Rashes are also commonly seen in pediatric practice, and

TABLE 7

COMPLICATIONS ENCOUNTERED IN THE ADMINISTRATION OF SULFADIMETHOXINE TO 590 INFANTS AND CHILDREN* IN A DOSE OF 1.0 GM./M.² INITIALLY, FOLLOWED BY 0.5 GM./M.² DAILY

Complication	Number	Percentage of total
Vomiting, mild	13	2.2
Vomiting, marked	3	0.5
Rash, morbilliform	5	0.8
Rash, urticarial	2	0.3
Transient leukopenia	1	0.1

* Patients from TABLES 5 and 6 plus 45 infants and children who received 7 to 10 days of therapy for prophylactic purposes.

their relation to the sulfadimethoxine therapy in this series cannot be established with certainty. In no case was the skin eruption persistent, hemorrhagic, or followed by desquamation.

We have carried out no studies on the absorption or toxicity of sulfadimethoxine in newborn or premature infants, and the experience of others suggests that information concerning sulfonamide toxicity from older infants and children is not applicable to this group.

Summary

Sulfadimethoxine appears to be a safe and effective chemotherapeutic agent for use in pediatric practice. It is well absorbed following oral administration, particularly when the microcrystalline-suspension dosage form is used. A single daily dose schedule is satisfactory for maintaining effective blood levels. A dosage schedule of 1.0 gm./m.² body surface area, followed by 0.5 gm./m.² daily is recommended for severe infections, and a schedule of one-half this dose is adequate for mild infections. Toxic reactions are infrequent and, in our experience, have not been serious.

NEWER SULFONAMIDES IN PEDIATRIC PRACTICE

Edward H. Townsend, Jr. and Agneta Borgstedt
Pediatric Service, Rochester General Hospital, Rochester, N. Y.

The sulfonamides enjoy an established place as antimicrobial agents effective against many bacterial invasions of the several body systems.[1-3] The accepted theory of their action is based on the postulate that sulfonamides act through interference with bacterial growth by displacing para-aminobenzoic acid.[4] Since the introduction of these drugs in the 1930s, investigators have continued the search for safer as well as more efficacious sulfonamide compounds and, more recently, their efforts have been directed to obtaining compounds capable of yielding therapeutic blood levels with minimal doses.

Two years ago one of us (E.H.T.) commented upon a paper[5] introducing a lipid emulsion of sulfisoxazole, a compound that, by enzymatic delay, provided therapeutic blood sulfonamide levels upon oral therapy twice a day. The following data concern a compound that has eliminated the disturbance of the flora in the digestive tract[6] and that provides adequate maintenance blood levels when administered but once daily.[7] The latter characteristic of the drug is most important in the practice of pediatrics, and not only because it facilitates medication in young patients. To cite one seeming side issue, there is the special case of the mother who works outside the home and cannot guarantee adequate therapy for a sick child at home. A medicinal compound of sufficient duration of action to provide sustained therapy assures treatment for the pediatric patient while the mother is at work.

In October, 1958, we presented a preliminary report upon experiences with sulfadimethoxine (Madribon*) before the Annual Symposium on Antibiotics.[8] At that time we mapped the deterioration curve of sulfadimethoxine (FIGURE 1) obtained in nonmedical hospital patients, which showed that therapeutic blood levels (7 mg. per cent) were maintained for more than 24 hours. Our original conclusions have been overwhelmingly confirmed by subsequent experience.

By the administration of an initial dose of 30 mg./kg. and a maintenance dose of 15 mg./kg. once daily thereafter, adequate therapeutic blood levels were maintained (FIGURE 2). Clinical trial[8] in 167 hospitalized and private patients with a variety of upper respiratory and gastrointestinal infections showed that sulfadimethoxine was 90 per cent effective in private patients and 84 per cent effective in hospitalized patients, ranging in age from less than 2 to 16 years. The failure in 10 per cent of the cases in the first group was probably due to the fact that the study was initiated in a season when viral infections are prevalent.

Since then, at least comparable success has been experienced in more than 500 patients in private practice. In such a large group, and particularly during the winter epidemics of upper respiratory diseases, control experiments in every case are naturally difficult to conduct. The function of the practicing physician is to treat the patients clinically with the best possible medication to achieve the earliest remission. Serum sulfadimethoxine levels were measured, however,

* Hoffmann-La Roche.

in all cases of failure with the medication. Since therapeutic blood levels were observed in these cases, failure could not be attributed to lack of absorption of the compound, but rather to lack of sensitivity of the responsible invading

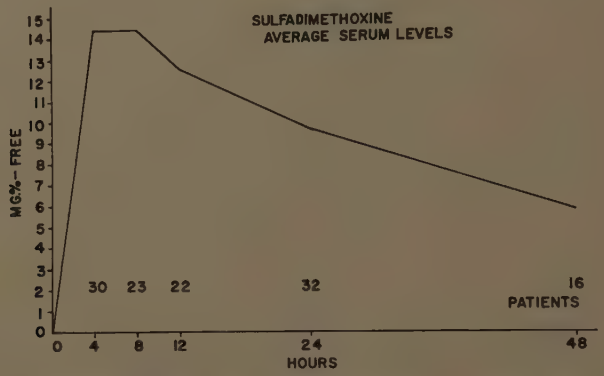


FIGURE 1. Deterioration curve after the administration of a single dose of sulfadimethoxine, 30 mg./kg. of body weight.

FIGURE 2. Serum sulfadimethoxine levels measured at random in 9 patients after an initial dose of 30 mg./kg. and a maintenance dose of 15 mg./kg. of body weight once daily.

agent. Despite failure of therapy in such instances, no evidence of toxic reaction had occurred in these or the remaining patients.

A young boy suffering from a vague illness characterized by high fever, headache, and malaise was given sulfadimethoxine. A mild exanthem appeared on the face, arms, and legs 24 hours later. A reaction to sulfadimethoxine was suspected, but in subsequent weeks many individuals with a similar rash were

observed who had not received sulfadimethoxine. Therefore, it is impossible to know whether this rash was due to the drug or was merely coincidental with its administration. No other generalized hematological reactions were encountered during this period.

This report deals with the use of sulfadimethoxine in the hospital treatment of infections proved or presumed to be of bacterial origin in 78 infants and children. Of these, 34 were treated after admission to the pediatric service of the Rochester General Hospital, while 44 were treated on an ambulatory basis in the outpatient department. The patients were selected after demonstrable evidence of bacterial infection. They were studied bacteriologically, hematologically, and by daily clinical examination throughout the period of study.

TABLE 1

RESULTS OF TREATMENT OF 44 CLINIC PATIENTS WITH MADRIBON*

Disease	No. of patients	Good response	Failure	Remarks
Otitis media and mastoiditis	17	13	4	2 resistant *Staph. aureus* 2 responses to Achromycin, 1 to Chloromycetin
Upper respiratory infection, pharyngitis, purulent rhinitis	16	16	1	
Bronchitis	2	2		1 addition penicillin
Pneumonia	3	3		2 addition penicillin
Tonsillitis and cervical adenitis	5	4	1	response to penicillin
Diarrhea	1	1		
Total	44	38	6	no side effects

* Total of clinic and ward patients was 78. A good response was found in 64 (82.1 per cent); failure resulted in 14 (17.9 per cent); and a questionable side effect was detected in 1 (1.2 per cent). Treatment was conducted at Rochester General Hospital.

All patients received an initial dose of sulfadimethoxine of 30 mg./kg. of body weight, and a maintenance dose of 15 mg./kg., administered once daily. Sulfadimethoxine levels were determined at 24 and 48 hours (in some cases oftener) to insure the attainment and maintenance of adequate serum sulfadimethoxine levels, according to the micromethod of Bratton and Marshall[9] as modified and standardized by Harold Rosenthal of the Rochester General Hospital.

Results

The results of treatment of 44 clinic patients with otitis media, mastoiditis, respiratory infections, tonsillitis, and adenitis (TABLE 1) indicate that therapy was effective in 82.1 per cent. The failures in treatment of otitis media, due to a resistant strain of *Staphylococcus aureus hemolyticus*, is in contrast to the results described in our preliminary report, which seemed to indicate that sulfadimethoxine was useful for treatment of "the resistant staphylococcus." Such staphylococci are classified as resistant when they grow *in vitro* in the presence

of penicillin and tetracycline. Apparently in some instances sulfadimethoxine is of benefit and in others it is not.

In the 34 ward patients (TABLE 2) the failure rate was 23.5 per cent. However, it is necessary to point out that these individuals were sufficiently ill to require hospitalization prior to institution of therapy. There was no significant bacterial spectrum that would make sulfadimethoxine more efficacious than other sulfonamides or, in many instances, than a broad-spectrum antibiotic. In the cultures of several patients the following organisms were grown: pneu-

TABLE 2
RESULTS OF TREATMENT OF 34 WARD PATIENTS WITH MADRIBON*

Disease	No. of patients	Good response	Failure	Remarks
Otitis media and mastoiditis	10	6	4	1 resistant *Staph. aureus* responding to erythromycin only 2 responding to Achromycin 1 responding to penicillin
Upper respiratory infection, pharyngitis, purulent rhinitis	4	3	1	
Bronchitis	1	1	1	
Genitourinary infection	8	6	2	1 (?) failure responded 24 hours after being placed on Gantrisin 1 response to Chloromycetin
Pneumonia	3	3		
Tonsillitis and cervical adenitis	4	4		1 developed maculopapular rash on penicillin and Madribon
Diarrhea	1	1		*Salmonella*—clinical symptom-free, but positive culture
Pyodermia	1	1		Bacitracin local
Sinusitis	1	1		
Prophylaxis for skull fracture extending to sinus	1	1		No infection developed
Total	34	26	8	1 (?) reaction

* At the Rochester General Hospital.

mococci, coliform bacilli, *Hemophilus influenzae*, and *Staph. aureus hemolyticus* of both resistant and sensitive strains. No one organism failed to respond at a higher rate than any other. It is, however, by a study of such failures that a better understanding of a drug's potential may be achieved. Thus, 2 failures in genitourinary infection may be due not to the specific infection, but rather to the fact that sulfadimethoxine, designed to maintain high blood levels for a protracted period, was not eliminated rapidly enough to ensure adequate antimicrobial urinary levels.

Failure in otitis media is not necessarily attributable to inadequacy of the antimicrobial agent used. The diagnosis is difficult, especially considering the problem of distinguishing between otitis media and myringitis in some cases, and between bacterial or viral etiology in others. The failure of 4 of 10 cases

of otitis media to respond to sulfadimethoxine may reflect the nature of the infection—that is, a bone-enclosed purulent infection in an area with relatively poor blood supply. Under these conditions therapeutic levels of sulfadimethoxine at the site of the infection are difficult to attain although, in all these

TABLE 3

SERUM SULFADIMETHOXINE LEVELS IN MOTHER AND INFANT WITH RELATION TO TIME BEFORE DELIVERY THAT SULFADIMETHOXINE WAS GIVEN TO MOTHER

Patient No.	Mother*	Sex of baby*	Interval after dose of 2.0 gm. to mother (min.)	Serum sulfadimethoxine level (mg. %)	
				Maternal blood	Cord blood
1	C.H. (152)	M (8^{7})	30	2.9	0.3
2	R.S. (153)	M (7^{13})	105	2.1	1.0
3	M.F. (233)	M (10)	116	6.3	3.3
4	G.A. (155)	M (7^{3})	120	10.4	3.1
5	E.H. (140)	F (7^{6})	140	5.5	2.1
6	N.M. (164)	M (7^{3})	150	0.3	0.3
7	J.A. (171)	F (8^{13})	150	2.2	0.6
8	R.B. (154)	F (8^{6})	160	3.0	1.8
9	D.H. (131)	F (7^{7})	165	7.7	3.8
10	E.Z. (132)	M (6^{11})	170	6.8	3.2
11	A.G. (215)	M (8^{11})	180	0.3	0.3
12	R.E. (162)	F (6^{4})	205	3.3	1.3
13	A.S. (173)	M (8^{3})	225	7.7	4.1
14	N.McE. (141)	F (6^{6})	230	4.7	2.3
15	S.W. (142)	F (8^{5})	233	10.7	10.4
16	A.B. (200)	F (7^{9})	250	5.9	3.3
17	E.Sc. (132)	F (7^{10})	250	2.3	1.7
18	P.K. (170)	M (8)	250	7.3	4.1
19	D.H. (153)	M (8^{2})	255	7.8	5.1
20	F.W. (135)	M (7)	264	2.3	1.2
21	D.O. (167)	M (8^{12})	325	5.7	3.7
22	P.A. (136)	F (5^{5})	330	15.3	17.6
23	J.B. (141)	M (5^{2})	345	10.7	7.5
24	M.S. (142)	F (5^{3})	385	12.7	13.0
25	A.P. (158)	M (6^{12})	390	3.0	1.9
26	P.F. (186)	F (8^{2})	461	13.0	13.4
27	J.P. (159)	M (6^{13})	465	1.0	1.0
28	H.T. (132)	F (7^{14})	485	11.6	9.8
29	S.F. (135)	M (9^{11})	810	11.7	15.3
30	D.W. (139)	M (8)	1440	11.7	10.7

* Figures in parentheses give weight in pounds for mother, and pounds and ounces (superscript number) for baby.

instances of failure, serum sulfadimethoxine levels of 12 mg. per cent or more had been obtained.

Thus, in the management of several serious bacterial infections in pediatrics, sulfadimethoxine has been used successfully in more than 86 per cent of the cases. No serious side reactions were observed. In 1 case a maculopapular rash developed, but could not be definitely attributed to sulfadimethoxine.

It seemed desirable that a compound that produces adequate blood levels for a protracted period be tried in the immediate *post partum* period. The pla-

cental transfer of sulfonamides and absorption during labor have been amply documented.[10-15] To test the transplacental transfer of sulfadimethoxine, 30 women in labor were administered 2 gm. of the drug, and blood levels in both the mother and newborn infant were determined. As can be seen in TABLE 3, placental transfer of the sulfonamide occurred within 5 hours, and adequate fetal blood levels were attained in the cord blood within that time.

A curious fact is that there was no consistent direct relationship between

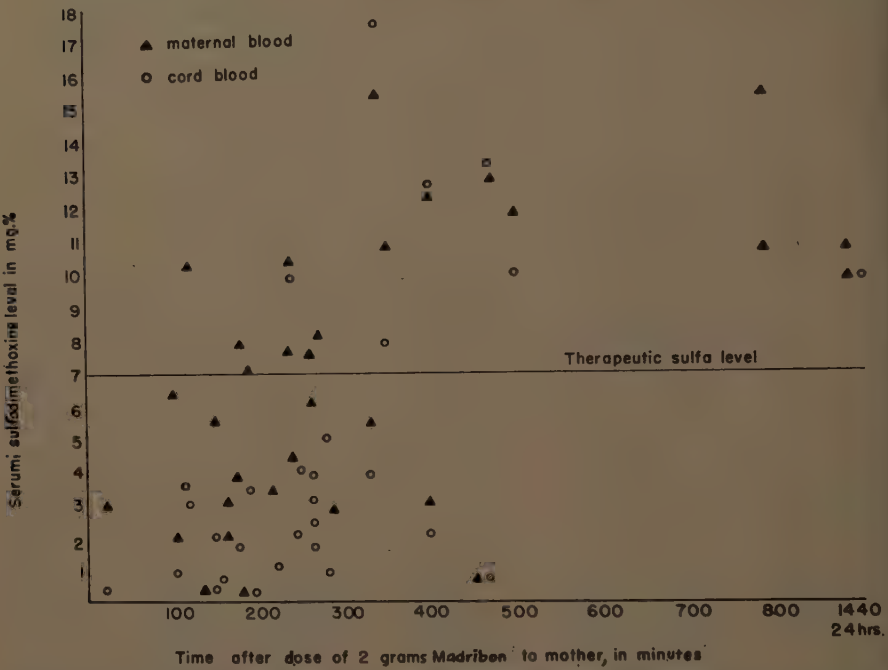


FIGURE 3. Relationship of the time of administration of 2 gm. sulfadimethoxine to mothers in labor and the serum levels in the mothers and infants. Adequate equal therapeutic levels may be expected in 5 hours.

TABLE 4

SERUM SULFADIMETHOXINE LEVELS IN MATERNAL AND CORD BLOOD AFTER ADMINISTRATION OF 2.0 GM. TO THE MOTHER

Patient No.	Interval after dose of 2.0 gm. to mother	Serum sulfadimethoxine level (mg. %)		Serum sulfadimethoxine level, baby (mg. %)				
		Maternal blood	Cord blood	Hours after birth 6	12	18	24	48
1	1 hr. 40 min.	3.0	1.8	1.2				
2	4 hr. 10 min.	7.3	4.1	2.8				
3	4 hr. 10 min.	2.3	1.7	1.5		1.3		
4	4 hr. 45 min.	1.0	1.0	0.6			0.3	
5	13 hr. 30 min.	11.7	15.3			13.0		
6	24 hr.	11.7	10.7				8.5	7.5

the serum level in the cord blood and that in the mother's. This fact remains unexplained. However, in 20 mothers and 8 infants, the levels were higher than 5 mg. per cent during the period of observation (FIGURE 3).

From the data in TABLE 4 it can be seen that the newborn is capable of maintaining adequate blood levels of sulfadimethoxine for 24 to 48 hours. This suggests that if the compound is administered to the mother it should protect the infant during the early neonatal period, before infection may become evident, and before the need for further therapy is investigated. However, the obstetrician should be cautioned that in the event of prematurity or hyperbilirubinemia sulfonamides may increase the likelihood of kernicterus[16, 17] by releasing the bilirubin from its protein-bound sites and allowing more rapid diffusion of the bilirubin to other body compartments, including the brain.

It may be used where indicated in obstetrics provided the obstetrician bears in mind this essential limiting factor. Sulfadimethoxine administered to the mother at or near term is capable of providing adequate therapeutic blood levels in the newborn for a sufficient period to allow the physician to search for a specific infection. This merits further investigation.

References

1. BRICKHOUSE, R. L., M. H. LEPPER, T. E. STONE & H. F. DOWLING. 1949. The treatment of penumonia and other infections with a soluble sulfonamide, Gantrisin (NU-445; 3,4-dimethyl-5-sulfanilamido-isoxazole). Am. J. Med. Sci. **218:** 133–137.
2. LOUGHLIN, E. H. & W. G. MULLIN. 1955. The relative absorption and elimination of sulfisoxazole and acetyl sulfisoxazole. Antibiotics and Chemotherapy. **5:** 609–615.
3. CARROLL, G. 1957. Current use of sulfonamides in urology. Ann. N. Y. Acad. Sci. **69**(3)**:** 395–398.
4. DAESCHNER, C. W., J. L. CLARK & E. M. YOW. 1957. A comparative evaluation of sulfonamides. J. Pediat. **50:** 531–551.
5. KRUGMAN, S. 1957. Clinical use of a lipid emulsion of sulfisoxazole. Ann. N. Y. Acad. Sci. **69**(3)**:** 399–403.
6. BAGDON, R. E., L. O. RANDALL & W. A. LEFF. 1959. Pharmacological studies with sulfadimethoxine. Ann. N. Y. Acad. Sci. **81**(2)**:** 3–9.
7. BOGER, W. P. 1959. A new long-acting antibacterial sulfonamide, 2,4-dimethoxy-6-sulfanilamido-1,3-diazine: a comparative study. Antibiotics Ann. N. Y. Med. Encycl. **:** 48–55.
8. TOWNSEND, E. H., JR. & A. BORGSTEDT. 1959. Preliminary report of clinical experience with sulfadimethoxine, a new long-acting sulfonamide. Antibiotics Ann. 1958–1959. **:** 64–68.
9. BRATTON, C. H. & E. K. MARSHALL, JR. 1939. A new coupling component for sulfanilamide determinations. J. Biol. Chem. **128:** 537–555.
10. BARKER, R. H. 1938. The placental transfer of sulfanilamide. New Engl. J. Med. **219:** 41.
11. SPEERT, H. 1938. Passage of sulfanilamide through human placenta. Bull. Johns Hopkins Hosp. **63:** 337–339.
12. SPEERT, H. 1942. Absorption of sulfonamides during labor. Surg. Gynecol. Obstet. **75:** 699–703.
13. LEE, H. M., R. C. ANDERSON & K. K. CHEN. 1938. Passage of sulfanilamide from mother to fetus. Proc. Soc. Exptl. Biol. Med. **38:** 366–368.
14. ZIAI, M. & M. FINLAND. 1957. Placental transfer of sulfamethoxypyridazine. New Engl. J. Med. **257:** 1180–1181.
15. SPEERT, H. 1943. Placental transmission of sulfathiazole and sulfadiazine and its significance for fetal chemotherapy. Am. J. Obstet. Gynecol. **45:** 200–207.
16. SILVERMAN, W. A., D. H. ANDERSON, W. A. BLANC & D. N. CROZIER. 1956. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. Pediatrics. **18:** 614–625.
17. ODELL, G. B. 1958. *In vitro* studies of the effect of sulfonamides on bilirubin (abstract). A.M.A. J. Diseases Children. **96:** 535.

Discussion

Saul Krugman (*New York University College of Medicine, Bellevue Medical Center, New York, N. Y.*): My experience with sulfadimethoxine has been limited to studies on absorption of the drug as measured by blood level determinations in approximately 50 infants—3 months to 1 year of age. Sulfadimethoxine was administered as a suspension (12.5 mg. per drop) in 3 dosage schedules: (1) 25 mg./kg. of body weight, single dose; (2) 25 mg./kg. every 24 hours; and (3) 25 mg./kg. initially, followed by 10 mg./kg. every 24 hours. Approximately 200 blood level determinations were performed.

Table 1
Blood Levels of Free Sulfadimethoxine*

Time interval (hours)	Blood level (mg. %)
4	6.4
8	8.5
24	5.4
48	2.4

* Single dose, 25 mg./kg.

Table 2
Blood Levels of Free Sulfadimethoxine

Time interval (days)	24-Hour blood levels* mg. %	
	A	B
1	4.6	5.3
2	6.6	5.1
3	8.0	5.5
4	6.7	5.0
5	6.1	5.0

* The values of Column A are for a dosage of 25 mg./kg. every 24 hours; each blood level is the mean of 11 determinations. Figures of Column B are for a dosage of 25 mg./kg. initially, followed by 10 mg./kg. every 24 hours; each blood level is the mean of 19 determinations.

The mean blood levels following the administration of a single dose (25 mg./kg.) of sulfadimethoxine are shown in table 1.

The mean 24-hour blood levels following multiple daily doses of sulfadimethoxine pediatric suspension are shown in table 2.

These studies indicated that adequate blood levels were achieved following the administration of sulfadimethoxine pediatric suspension to infants 3 months to 1 year of age in a dose of 25 mg./kg. of body weight, followed by either 25 or 10 mg./kg. every 24 hours.

The following precaution re-emphasizes a point made by Daeschner concerning the administration of sulfadimethoxine to infants less than 3 months of age. The drug was not given to premature or newborn infants for two reasons: sulfadimethoxine is excreted predominantly as a glucuronide, and human premature

and newborn infants appear to have an ineffective mechanism for the conjugation of glucuronides. Accordingly, toxic blood levels may result from the lack of formation of conjugation products, with subsequent impairment of excretion. The various organs of the infant, particularly the liver and kidney, have matured adequately by 3 months of age to insure normal detoxification and excretion of the drug.

No untoward effects were noted in the 50 infants who received sulfadimethoxine.

USE OF MADRIBON* IN DERMATOLOGICAL CONDITIONS, WITH SPECIAL REFERENCE TO ACNE

S. William Levy

Division of Dermatology, Department of Medicine, University of California, San Francisco Medical Center, San Francisco, Calif.

Dermatological conditions are seen by every practitioner, and treatment of acne is the major activity of most dermatological practices.[1] It has been variously estimated that one half the population is subject to acne;[2] that 90 per cent of all teen-agers are afflicted with this condition, usually more severe in boys than girls;[3] and that acne is found in so many young persons as to be practically a physiological manifestation of puberty and abnormal at this age only when obviously noticeable.[4]

Although most often caused by the physiological changes during puberty and adolescence, acne has its greatest impact on the psychological adjustment of the individual. Referring to the emotional trauma that may be produced by severe cases of acne, Rothman[5] has described it as a condition which, while it does not endanger life, may ruin it.

Facial acne is by far the commonest type until the age of 17 or 18, slowly regressing through the thirties, but often leaving scars. The pustular acne is responsible for much of the permanent destructive skin damage. When beard hair in men becomes well established, facial acne diminishes, and the predominant site of eruption tends to be localized on the trunk.[4]

In a study on the histogenesis of acne it was found that the earliest changes occurring in the skin were hyperkeratinization of the excretory duct of the sebaceous gland, which results in the deposition of a keratinous plug in the follicular neck.[6] In the event of a secondary infection, the follicle comes to resemble a septic abscess.[7] These follicular openings must be kept free of foreign matter by well known hygienic measures; when infected, the use of antibacterials is demanded.

The nasopharynx has been regarded as the source for the micrococci found in acne pustules.[8] The most common pathogens are staphylococci. While antibiotics have been effective in many cases, increasingly resistant strains of staphylococci have developed in patients treated for three months or longer. However, stubborn cases of acne require prolonged treatment,[9] for the longer the improvement of acne lesions can be sustained, the less will be the likelihood of a relapse. Consequently, there is need of an antimicrobial agent that will satisfy a multiplicity of requirements in the treatment of the pustular phase of this disorder. Such a drug must possess broad spectrum activity and low tolerance and resistance liability in spite of prolonged treatment; it must also be reasonably free of systemic side effects and produce a minimum of skin sensitivity reactions. Other investigators,[10] as well as we, have found that a course of sulfonamide therapy is often effective. The results of a current study with a new antibacterial sulfonamide employed in pustular skin conditions in our dermatological practice follow.

Madribon (2,4-dimethoxy-6-sulfanilamido-1,3-diazine) has been found

* Product of Hoffmann-La Roche Inc., Nutley, N. J.

quite active in animal infections caused by staphylococci.[11] Clinically, Leming *et al.*[12] obtained dramatic results also when they administered the drug to 5 members of one family, who had had repeated episodes of furunculosis that resisted other forms of therapy. We, therefore, included in this study a number of other dermatological disorders in addition to those of patients suffering with acne.

Materials and Methods

A total of 44 patients with various pyogenic skin conditions (TABLE 1) was treated with Madribon. All but one received a maintenance dose of 0.5 gm daily. This patient was given 4 cc. of a 5 per cent suspension, instead of the tablets. Thirty of the patients were acne cases, with an age range of from 15

TABLE 1
RESULTS OF TREATMENT WITH MADRIBON*

Diagnosis	No. of patients	Results			
		Excellent	Controlled	Fair	Poor
Acne vulgaris	30	8	17	5	
Folliculitis and furunculosis	3	3			
	2	1			1
Pyogenic abscesses	1	1			
Neurotic excoriations with secondary pyogenic infection	2	2			
Pyogenic infection of hands	1	1			
Infected eczema (seborrheic, dyshidrotic)	3			3	
Sycosis barbae	1		1		
Furuncle on back	1	1			
Total	44	17	18	8	1

* Excellent and satisfactory results were achieved with 80 per cent of the cases, fair results with 18 per cent, and failure in 2 per cent. There were no side effects, except in a patient who was also on barbiturate therapy.

to 36 years, averaging 23.4 years. The age range in the remaining 14 patients, with such disorders as folliculitis, eczema, and furuncles, was from 14 to 58 years, with an average of 42. While in 1 patient, treatment was discontinued after 5 days because of clearing of the secondary infection associated with excoriations, the remaining patients all received treatment for from 10 to 60 days.

Adjunctive therapy consisted of the usual measures. The patients were instructed to wash several times a day with a detergent soap or emollient, using just sufficient pressure to cause a slight degree of continuous peeling and to dislodge the comedo plugs. Dietary restrictions were also recommended when these seemed necessary.

Results

Eight of the 30 acne patients showed excellent clearing of the pustular lesions, 17 were well controlled on Madribon therapy, and 5 had only fair results. Of

the remaining patients, 9 had excellent results, 1 good results, 3 fair, and 1 poor. The 3 who had only fair results had eczema with secondary infections. However, in 1 patient with dyshidrotic eczema, the secondary infection cleared totally; this was the case of the 14-year-old girl who had received the Madribon suspension. The patient who had poor results was given Madribon for furunculosis in the groin. At the time, he was also taking a barbiturate to help him sleep. After 10 days it became necessary to discontinue the Madribon because of a sensitivity reaction. When seen 4 days later, he had severe erythema multiforme of the hands and feet. The condition cleared with the administration of ACTH. There were no other adverse reactions in this group; the results are summarized in TABLE 1.

Comments and Conclusions

The search for effective drugs in the treatment of pustular acne and other skin infections of both primary and secondary origin continues for 2 reasons: (1) the cost of antibiotic administration, especially in view of the protracted treatment these conditions require; and (2) the development of resistant bacteria. Sulfonamides have been found to effect clearing of pustular conditions.

Madribon, a new antibacterial of the sulfa group, was administered to 44 patients with various pyogenic skin conditions, chiefly acne vulgaris. On an oral dose of 0.5 gm. daily the condition was controlled, sometimes dramatically, in 80 per cent of the cases. Eighteen per cent showed some improvement, and in only 1 patient was the result poor. Except for the latter, who was simultaneously receiving a barbiturate, no side reactions were noted.

The once-a-day oral administration is a great advantage with patients who are essentially ambulatory, and who often must continue therapy for weeks and even months.

On the basis of this limited experience, Madribon can be regarded as a clinically effective and well-tolerated drug for the treatment of infected skin lesions. Continued trials in dermatological conditions of this nature are believed warranted.

References

1. SULZBERGER, M. B. 1953. Discussion of F. T. Becker: The acne problem. Arch. Dermatol. and Syphilol. **67:** 173.
2. HINRICHSEN, J. & A. C. IVY. 1938. Incidence in Chicago region of acne vulgaris. Arch. Dermatol. and Syphilol. **37:** 975.
3. POIRIER, P. 1957. Acne and its treatment. Can. Med. Assoc. J. **77:** 866.
4. MACKENNA, R. M. B. 1957. Acne. Lancet. **1:** 169.
5. ROTHMAN, S. 1955. Acne vulgaris. Guest editorial. J. Am. Med. Assoc. **159:** 1124.
6. VANSCOTT, E. J. & R. C. MACCARDLE. 1956. Keratinization of the duct of the sebaceous gland and growth cycle of the hair follicle in the histogenesis of acne in human skin. J. Invest. Dermatol. **27:** 405.
7. GRANT, R. N. R. 1957. The relationship between acne and hair growth. A.M.A. Arch. Dermatol. **76:** 179.
8. STRITZLER, C. & L. FRANK. 1958. Significance of the response of acne vulgaris to antibiotics. Antibiotic Med. & Clin. Therapy. **5:** 109.
9. ROBINSON, M. M. 1958. Treatment of acne vulgaris with tetracycline-nystatin and tetracycline. Antibiotics Ann. 1957–1958. : 451.

10. Andrews, G. C., A. N. Domonkos & C. F. Post. 1951. Treatment of acne vulgaris. J. Am. Med. Assoc. **146:** 1107.
11. Fust, B. & E. Boehni. 1959. Tolerance and antibacterial properties of 2,4-dimethoxy-6-sulfanilamido-1,3-diazine (Madribon) and some other sulfonamides. Antibiotic Med. & Clin. Therapy. Suppl. 1. **6:** 3.
12. Leming, B. H, Jr., C. Flanigan, Jr. & B. R. Jennings. 1959. Clinical evaluation of sulfadimethoxine (Madribon), a wide-spectrum antibacterial. Antibiotic Med. & Clin. Therapy. Suppl. 1. **6:** 32.

THE USE OF SULFADIMETHOXINE (MADRIBON*) IN THE TREATMENT OF PAPULOPUSTULAR AND CYSTIC ACNE VULGARIS

Milton M. Cahn and Edwin J. Levy

Department of Dermatology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Acne vulgaris in varying degrees of severity affects 90 per cent of adolescents[1] and constitutes about one seventh of the skin disorders seen in dermatological practice.[2]

Although a disorder of multiple origin,[3, 4] acne is essentially the result of hormonal imbalance,[5] coincident with adolescence.[4-7] The fact that acne occurs in girls administered progesterone and in women with masculinizing tumors or under androgen treatment, but not in eunuchs, is presumptive evidence that this disorder stems from androgen-estrogen imbalance.[4] Because it flares with emotional tension, the psychogenic factor must also be considered in its causation.[4, 8]

The basic pathological changes are in the pilosebaceous apparatus.[4, 8, 9] If an acne lesion is observed from its onset, it is seen to begin as a comedo or "blackhead", which is a hard mass of keratin and sebum blocking the dilated follicular orifice.[10, 11] This comedo may increase in size and ultimately rupture the delicate wall of the follicle. Keratin and sebum then escape into the corium and set up a foreign body reaction. Clinically, these changes are manifested by various stages from erythematous follicular papules to pustular and cystic lesions.

The normal intact skin is resistant to invasion by most bacteria. The skin, however, is never sterile, but supports a luxuriant growth of nonpathogenic organisms comprising the so-called resident flora; this consists of aerobic micrococci and *Corynebacterium*, and anaerobic *Micrococcus saccharolyticus* and *Propionibacterium acnes*, the latter 2 outnumbering the aerobic organisms by 10 to 100 times. Pathogenic bacteria also reside temporarily on the skin surface, but the natural defenses of the intact skin adequately control them.

Present knowledge indicates that acne is not primarily a bacterial disease. In fact, in most acne patients it can be demonstrated that the early pustule is sterile. If the conditions are favorable, however, pathogens or possibly even normally nonpathogenic organisms may cause infection in the previously sterile acne lesion. While infection per se may not prolong the course of acne vulgaris, it certainly adds to the embarrassment and emotional stress of the adolescent threatened with acne scarring and permanent disfigurement.

Several chemotherapeutic agents have been used in recent years for the treatment of acne vulgaris in an attempt to prevent the skin damage that results from infection during the pustular stage.[8] Accounts have been published of the beneficial effects of long-term use of broad-spectrum antibiotics in this disease.[2, 8, 12-14] However, certain side effects have imposed distinct limitations on their use.[4, 15] One of the more serious drawbacks has been the emergence of resistant strains of bacteria;[16-19] thus, the antibiotics often become

* Product of Hoffmann-La Roche Inc., N. J.

ineffective when they are required for the treatment of serious systemic bacterial disease. The sulfonamides also have been used,[9, 20] and they too have not been without disadvantage; the earlier shorter-acting compounds required frequent dosage, and the longer-acting compounds sometimes caused severe side reactions.[21-26]

Reports of the efficacy and safety of a new long-acting sulfonamide,[27-29] sulfadimethoxine (Madribon), prompted this investigation, which was undertaken to determine the drug's value in the treatment of patients with pustular and cystic acne vulgaris.

Case Material and Method

One hundred thirty-four patients with pustular and cystic acne vulgaris were included in this study. They constituted problem cases in which the acne was of at least 1 year's duration; many had been under treatment for from 2 to 5 years. The age range was 15 to 41 years, and 80 per cent were females.

The double-blind method of study was used in which Madribon and placebos were administered in successive courses of therapy in the same patient. On a random basis the patients were divided into two groups, one receiving first the medication (labeled M_1), and the other the placebo (labeled M_2). At the end of the first experimental period the order was reversed; thus, each patient served as his own control.

TABLE 1
RELATIVE EFFECTIVENESS OF SULFADIMETHOXINE AND PLACEBO

Sulfadimethoxine Effective		Placebo and sulfadimethoxine Equally effective		Neither effective	
No. of patients	%	No. of patients	%	No. of patients	%
75	55.97	22	16.42	37	27.61

During the first week of treatment, the dose was 1 gm. (2 tablets) of either the drug or the placebo administered b.i.d. For 4 weeks thereafter the dose was 0.5 gm. (1 tablet) daily. After 5 weeks on M_1, Group I was shifted to M_2, and Group II from M_2 to M_1 for another 5 weeks, and with the same dose schedule.

No hormones, vitamins, or other systemic medications were prescribed. Local therapy consisted of cleansing with soap and water, application of acne lotion, and exposures to a Westinghouse sun lamp (FS 40). None of the patients received X-ray treatment.

White blood counts, differential stains, and routine urinalyses were done weekly on all patients.

Results

The results of therapy summarized in TABLE 1 show that Madribon produced marked improvement in 75 (56 per cent) of the patients; placebo and Madribon

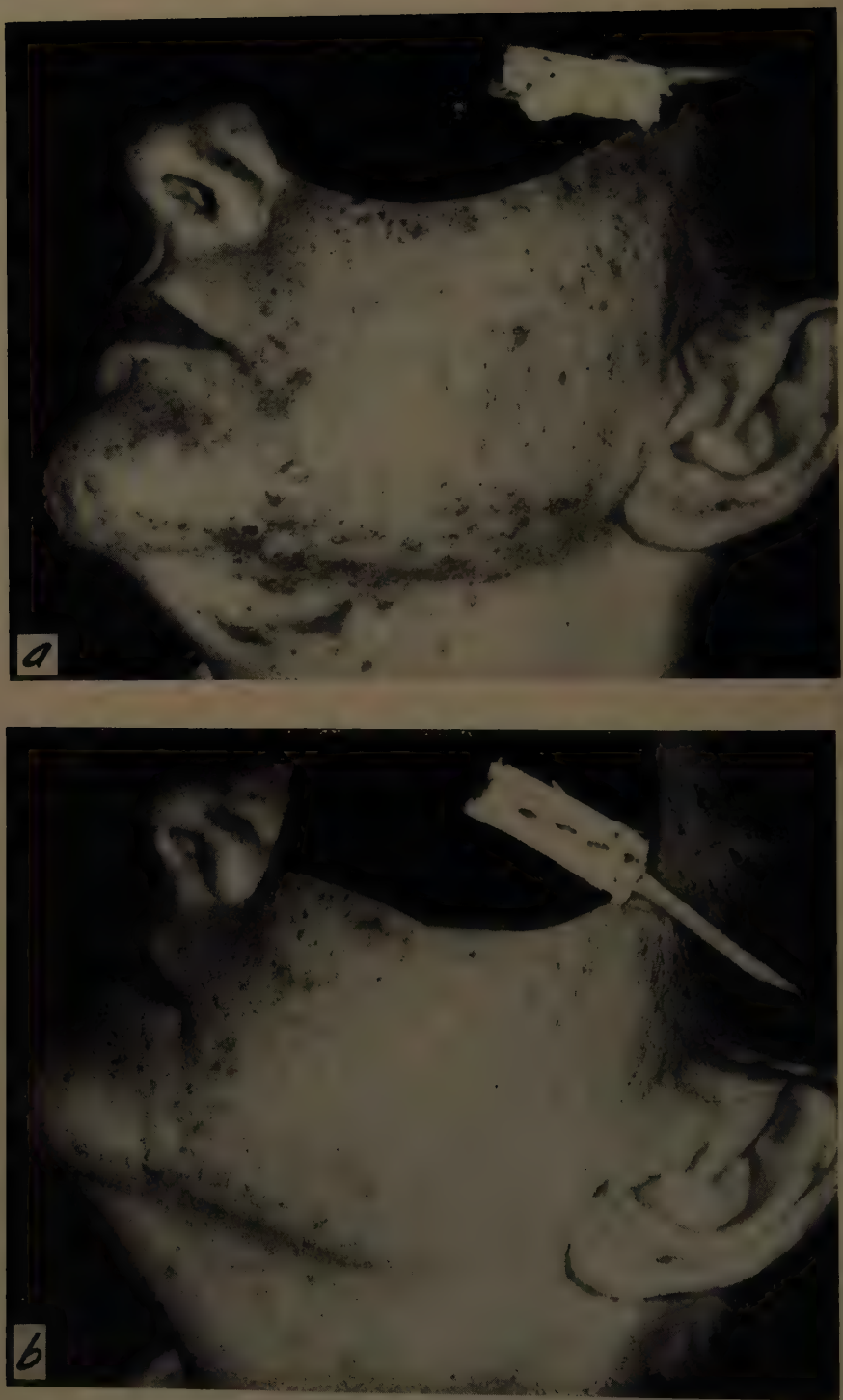


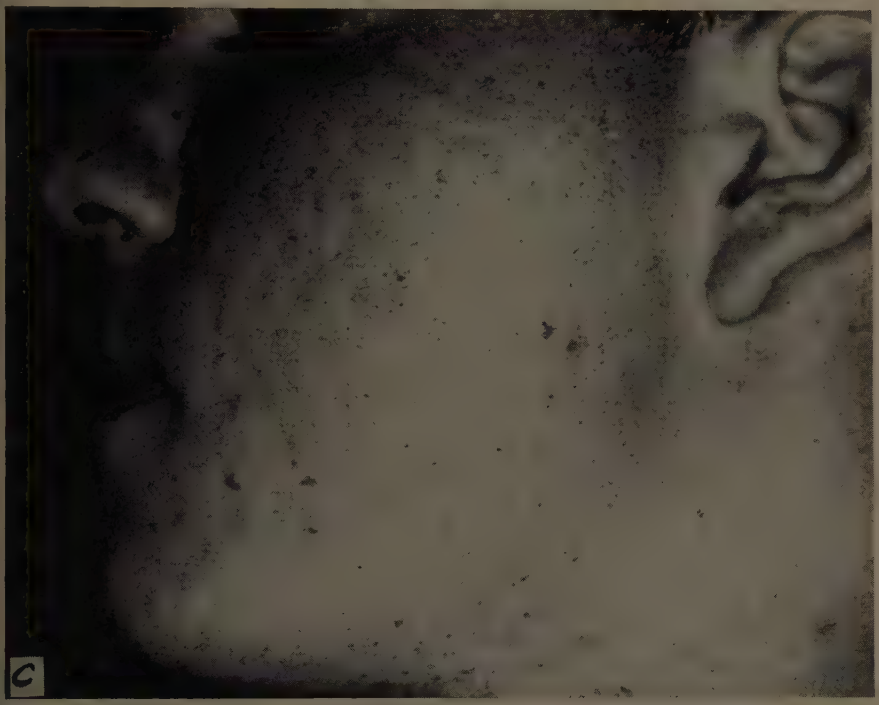
FIGURE 1. (*a*) Severe pustular and cystic acne in a 27-year-old female. (*b*) After 4 weeks of therapy.

administration was equally effective in 22 (16.4 per cent); and neither the active drug nor the placebo was effective in 37 (27.6 per cent) of the cases. The two case histories cited below illustrate the characteristic response to treatment. A 27-year-old female manifested excellent results during the course of Madribon therapy (FIGURE 1). She was then placed on placebo and within 1

FIGURE 2. Bacterial sensitivity study showing marked *in vitro* sensitivity to Madribon.

week there was a flare of the acne, which increased during the next 4 weeks. She was then given Madribon again, with relatively prompt improvement. A 17-year-old male with severe acne had not improved with previous antibiotic medications. The course of placebo therapy (M_2) was also without improvement. A bacterial sensitivity study (FIGURE 2) showed marked *in vitro* sensitivity to Madribon. He was placed on Madribon and within 2 weeks there was marked improvement (FIGURE 3). At the end of 5 weeks his skin was almost completely clear.

FIGURE 3. (*a*) Pustular acne in a 17-year-old male. (*b*) Improvement shown within 2 weeks of Madribon therapy. (*c*) After 5 weeks of Madribon therapy the skin is almost completely clear.



No signs of toxicity were noted. Laboratory tests were negative in all instances as determined by the absence of abnormal findings in the blood studies and urinalyses. There was no evidence of photosensitivity to sun lamp exposures of the face, neck, and back.

Discussion

If one is to use an antibiotic agent in the treatment of pustular and cystic acne vulgaris, it is necessary to find one that has a high degree of effectiveness without producing untoward side reactions or resistant organisms during the long-term therapy required in the management of the disease.

Evaluated by these criteria, Madribon has produced favorable results in this series of patients even though more than one fourth of the group was not benefited. However, in a critical evaluation such as this, 56 per cent effectiveness must be considered a more than satisfactory over-all result. The favorable response seen in one sixth of the patients on the placebo is not surprising, particularly since psychogenic factors play a role in the etiology of the disorder.

It would seem most logical that Madribon works by virtue of its antibacterial action. However, pending further fundamental knowledge of the role of bacteria in the causation of acne and the possible metabolic effects of chemotherapeutic agents beyond their antibacterial action, the final answer as to why Madribon is effective is conjectural.

Summary

Sulfadimethoxine (Madribon), a new long-acting and low-dosage sulfonamide, was evaluated in a double-blind study of 134 patients with pustular and cystic acne.

The patients were placed on the drug or placebo for a 5-week period, and then shifted to the other for the second 5-week period of the study.

Madribon was effective in 56 per cent of the patients; Madribon and placebo were equally effective in 16.4 per cent; neither the active drug nor the placebo was effective in the remaining 27.6 per cent.

No untoward reactions were noted clinically or by laboratory tests on blood and urine.

Madribon appears to be a useful and safe chemotherapeutic agent in the treatment of pustular and cystic acne vulgaris.

References

1. Poirier, P. 1957. Acne and its treatment. Can. Med. Assoc. J. **77:** 866.
2. Robinson, M. M. 1958. The status of antibiotic therapy in acne. Antibiotic Med. & Clin. Therapy **5:** 293.
3. Way, S. C., G. C. Andrews & A. N. Domonkos. 1957. Topical hydrocortisone therapy in acne rosacea and acne vulgaris. N. Y. State J. Med. **57:** 3463.
4. Rattner, H. 1959. Acne—the situation at present. Postgrad. Med. **25:** 446.
5. Sulzberger, M. B. & R. L. Baer. 1949. Acne vulgaris and its management. Year Book of Dermatol. and Syphilol. : 9–39.
6. MacKenna, R. M. B. 1957. Acne. Lancet. **1:** 169.
7. Baird, J. N. 1958. Acne, a new approach to an old problem. J. Pediat. **52:** 152.
8. Robinson, M. M. 1958. Treatment of acne vulgaris with tetracycline nystatin and tetracycline. Antibiotics Ann. 1957–1958 : 451–455.
9. James, K. W. & J. B. Tisserand, Jr. 1958. Treatment of acne vulgaris. GP **18:** 131.
10. Cohen, E. L. 1956. Mechanism of comedo formation in acne vulgaris. Brit. J. Dermatol. **68:** 362.
11. Van Scott, E. J. & R. C. MacCardle. 1956. Keratinization of the duct of the sebaceous gland and growth cycle of the hair follicle in the histogenesis of acne in human skin. J. Invest. Dermatol. **27:** 405.
12. James, A. P. R. 1958. Antibiotic combination therapy of severe acne vulgaris. Ohio State Med. J. **54:** 903.
13. Cronk, G. A., D. E. Naumann, E. J. Heitzman, F. N. Marty, K. J. McDermott & A. A. Vercillo. 1956. Tetracycline hydrochloride in the treatment of acne vulgaris. A.M.A. Arch. Dermatol. **73:** 228.
14. King, W. C. & M. A. Forbes, Jr. 1956. The use of tetracycline in the treatment of acne vulgaris: a clinical study. Southern Med. J. **49:** 875.
15. Becker, F. T. 1953. The acne problem. Arch. Dermatol. and Syphilol. **67:** 173.
16. Weil, A. J. 1958. Increased resistance to antibiotics among microorganisms isolated in a general hospital (1956–1957). N. Y. State J. Med. **58:** 3102.
17. Herrell, W. E. 1958. Hazards of antibiotic therapy. J. Am. Med. Assoc. **168:** 1875.
18. Yow, M. D., M. M. Desmond & L. N. Nickey. 1959. The management of staphylococcal disease in infants and children. J. Pediat. **54:** 409.
19. Welch, H., C. N. Lewis, H. I. Weinstein & B. B. Boeckman. Severe reactions to antibiotics: a Nation-wide survey. Antibiotics Ann. 1957–1958. : 296.
20. Lehr, D. 1955. Present status of sulfonamide therapy. Modern Med. : 111.
21. Tisdale, W. A. 1958. Focal hepatitis, fever and skin rash following therapy with sulfamethoxypyridazine, a long-acting sulfonamide. New Engl. J. Med. **258:** 687.
22. Hershfield, B. M. & J. J. Stern. 1958. Toxic reaction to sulfamethoxypyridazine (Kynex). N. Y. State J. Med. **58:** 1508.
23. Schwartz, M. J. & W. S. Norton. 1958. II. Thrombocytopenia and leukopenia associated with use of sulfamethoxypyridazine. J. Am. Med. Assoc. **167:** 457.
24. Blanchard, A. J. & G. A. Mertens. 1958. Hypersensitivity myocarditis occurring with sulfamethoxypyridazine therapy. Can. Med. Assoc. J. **79:** 627.

25. Holsinger, D. R. *et al.* 1958. Fatal aplastic anemia following sulfamethoxypyridazine therapy. Proc. Staff. Meeting Mayo Clinic. **33:** 679.
26. Perry, H. O., & R. K. Winkelmann. 1959. Adverse reactions to sulfamethoxypyridazine (Kynex). Its use in the treatment of dermatitis herpetiforme. J. Am. Med. Assoc. **169:** 111.
27. Townsend, E. H., Jr. & A. Borgstedt. 1959. Preliminary report of clinical experience with sulfadimethoxine, a new long-acting sulfonamide. Antibiotics Ann. 1958–1959. : 64.
28. Elia, J. C. 1959. Preliminary report on a new antimicrobial agent, sulfadimethoxine (Madribon), in the treatment of respiratory and chronic ear infections. Antibiotic Med. & Clin. Therapy. **6** (Suppl. 1) : 61.
29. Leming, B. H., Jr., C. Flanigan, Jr. & B. R. Jennings. 1959. Clinical evaluation of sulfadimethoxine (Madribon), a wide-spectrum antibacterial. Antibiotic Med. & Clin. Therapy. **6** (Suppl. 1) : 32.

THE BACTERIOLOGICOCLINICAL EVALUATION OF 2,4-DIMETHOXY-6-SULFANILAMIDO-1,3-DIAZINE (MADRIBON*) IN VARIOUS UROLOGICAL DISORDERS ASSOCIATED WITH URINARY TRACT INFECTION†

Michael Sierp and John W. Draper

Department of Surgery, Cornell University Medical College and Second (Cornell) Division of Urology, Bellevue Hospital, New York, N. Y.

The systemic treatment of urinary tract infections has received a great deal of attention during the past three decades. A host of chemotherapeutic agents has been introduced to the modern armamentarium of every clinician to eradicate these infections as quickly and as efficiently as possible. In spite of this, the over-all results of the antimicrobial therapy of urinary tract infections are very disappointing. The treatment is frequently difficult, protracted, and frustrating for the patient as well as for the doctor. A rapidly increasing number of drug-resistant organisms, the high incidence of hypersensitivity and toxic reactions to various antimicrobial agents, and superimposed infections with occasional fatality are well-known complications of treatment with antibiotics. These unfortunate observations have stimulated great interest and effort in further search for safer and better-tolerated antimicrobial compounds that could be used effectively against a variety of Gram-positive as well as Gram-negative bacterial infections.

Madribon is one of the sulfonamides that has been developed recently and has demonstrated *in vitro* evidence of usefulness against antibiotic-resistant staphylococci and some strains of *Proteus* and *Escherichia coli*. Furthermore, this new compound is found to possess several additional characteristics, unknown in older sulfonamides, that make it more desirable for clinical usage. It is readily absorbed from the gastrointestinal tract, poorly acetylated, and slowly excreted in the urine in the form of an active sulfonamide. The effective concentrations are sustained in the blood at dosages much lower than those needed with most other familiar sulfonamides. For these reasons a bacteriologicoclinical evaluation of 2,4-dimethoxy-6-sulfanilamido-1,3-diazine in various urological disorders associated with infection has been undertaken.

Materials and Methods of Study

General material. 2,4-Dimethoxy-6-sulfanilamido-1,3-diazine is a white, odorless, and tasteless crystalline powder. The solubility lies between 4.6 and 7.2 mg./100 ml. in the *p*H range of 3.1 to 5.74. This new sulfonamide was found to be effective against many Gram-positive and Gram-negative microorganisms *in vitro*.[6] Staphylococci showed a high sensitivity to the drug in minimal concentration, and beta-hemolytic *Streptococcus* and Type 1 *Pneumococcus* were inhibited by somewhat higher concentration. Among the Gram-negative organisms, *E. coli*, the *Klebsiella* group, and various *Salmonella* species exhibited relatively higher sensitivity. A rather poor antibacterial activity

* Product of Hoffmann-La Roche Inc., Nutley, N. J.

† The investigation reported in this article was supported in part by a grant from Lasdon Foundation and in part by a grant from Hoffmann-La Roche Inc.

was observed against *Pseudomonas aeruginosa*. Studies show that it is well tolerated by experimental animals.

Madribon is excreted slowly during an 8-day period and more than 80 per cent is recovered in the urine, mostly in metabolized form. It is readily conjugated and excreted as a highly soluble glucuronide. The blood levels have been shown to reach a maximum within 12 hours after oral administration and to decline gradually with an average half life of 36 hours.[5]

Method of clinical study. For the purpose of more accurate study, subjects were segregated into three groups: (1) ambulatory patients from the outpatient department; (2) hospital ward patients; and (3) patients maintained on catheter drainage or utilizing other urinary appliances. The diagnostic program included a careful evaluation of medical history with special attention to previous urinary tract infections, determination of blood urea nitrogen, a blood count, intravenous pyelography and, if indicated, cystoscopic examination. Urine was obtained at the initial examination for culture, sensitivity study, and colony counts. Following this preliminary study all patients were given 2 gm. of Madribon orally for the first day and then 1 gm. for 8 more days, for a total of 10 gm. Patients were examined at biweekly intervals with urinalysis, smear of urinary sediment, colony counts, and determinations of concentrations of Madribon in the blood and urine. On each visit, data were elicited concerning the symptoms from urinary tract infection and also untoward effects from the drug. The therapeutic efficacy of Madribon was appraised by the disappearance of symptoms, lowering of fever, absence of pyuria, and normality of blood count. The clinical response of the therapeutic regime was classified as "good" if during 4 weeks after discontinuing treatment the patient remained asymptomatic, had no pyuria, and demonstrated 2 sterile urine cultures. The response was considered "fair" if clinical and bacteriological improvement was manifested within the first days of treatment, but relapses occurred during or at the end of the 4-week period of observation. Persistence of pyuria and positive urine culture with only slight or no clinical improvement was recorded as "no response to treatment." Patients maintained on catheter drainage or utilizing urinary incontinence appliances were classified on the basis of clinical observation and grouped either as improved or failure.

Methods of study in vitro. Samples were obtained from the midstream voided urine or from a catheter if the patient was unable to void. The sediment of the urine was examined for bacteria, cellular components, casts, and crystals. Pyuria was considered to be present if 5 or more leukocytes per high-power field were observed in the noncentrifuged urine. Inoculation was done promptly, except for evening urine, which was stored in the refrigerator overnight. This consisted of seeding 0.1 ml. of vigorously shaken urine onto the blood agar plate and incubating it overnight. If, on microscopic examination, moderate or severe pyuria was observed and many bacteria were seen, appropriate dilutions were prepared and cultured as described above. The bacterial growth was estimated (after consideration of the dilution factor) according to the number of colonies seen on the agar plate. The rest of the specimen was centrifuged for 10 min. and, after decantation, inoculated into the broth and various media for identification of the organisms. Readings were obtained after overnight incubation.

The minimum inhibitory concentration of Madribon for various organisms was determined by the conventional technique of serial dilution tests in the semisynthetic medium of Adams and Roe. The inoculum consisted of 0.05 ml. of a 10^{-3} diluted broth culture but, in the case of streptococcal or pneumococcal infections, the same volume of 10^{-1} diluted culture was used. The drug was dissolved in alkali to give a solution with a *p*H of 9.0. Readings were obtained after 24 hours of incubation.

The antibacterial effect of Madribon on organisms in the urine was based on the results of cultures and quantitative estimation of bacterial growth. The organism was considered "eradicated" if no growth was observed on follow-up cultures and classified as "persistent" if the posttreatment cultures demonstrated some growth nearly equal in quantity to the pretreatment organisms. Strains that grew on follow-up cultures but demonstrated at least tenfold reduction in colony counts were classified as "suppressed."

Concentrations of free and total Madribon in the blood and urine were assayed by the method of Bratton and Marshall[1] on protein-free filtrates.

Case Material

Patients selected for the study were all men with urinary tract infections. The majority of these cases were associated with prolonged catheter drainage for urinary incontinence or obstruction due to prostatic hypertrophy, long-standing urethral strictures, and chronic renal conditions. A total of 59 patients was studied during a period of 4 or more weeks. They varied in age from 17 to 85, with the majority in the fifth and sixth decades of life.

There were 38 ambulatory patients with acute and chronic urinary tract infections. Approximately 50 per cent of them had had some surgical procedures in the past and had been treated with various antimicrobial agents intermittently.

The hospital group consisted of 21 patients, 79 per cent of whom had had some type of prostatic surgery prior to Madribon treatment. Four patients had had other surgical procedures, and 1 was treated for chronic pyelonephritis following cystectomy and cutaneous urinary diversion. In contrast to the ambulatory patients, these cases were complicated by drainage tubes, calculi, and protracted urinary tract infections.

The types of infection and distribution of organisms isolated at the time of the initial evaluation are presented in TABLE 1. The variety of the species involved in the urinary tract infections is clearly demonstrated. A single isolate was recovered in 39 of the 59 patients. The remaining 20 demonstrated 2 or more species on pretreatment cultures. The most common offending organisms encountered during this study were *B. proteus*, *gamma-Streptococcus* (*Enterococcus*), and *E. coli*, in this order. Enterococci dominated as the offending organisms in the infections with single species, and *B. proteus* was most frequently seen in mixed infections. *Aerobacter aerogenes* and *Pseudomonas aeruginosa* were observed in only a few instances.

The sensitivity of various bacteria as determined by the tube dilution is presented in TABLE 2. Of 91 strains examined *in vitro*, 49.1 per cent were inhibited

TABLE 1
TYPES AND DISTRIBUTION OF INFECTING ORGANISMS

Infecting organisms	Number of infections
Infections with one species	
E. Coli	3
Proteus species	7
Coliform species	2
A. aerogenes	5
Pseudomonas aeruginosa	2
Alpha-Streptococcus	—
Beta-Streptococcus	—
Gamma-Streptococcus	10
Staph. aureus	8
Staph. albus	2
Subtotal	39
Infections with two species	
B. proteus and *E. Coli*	3
B. proteus and *A. aerogenes*	1
B. proteus and *alpha-Streptococcus*	1
B. proteus and *gamma-Streptococcus*	3
B. proteus and *Staph. albus*	1
A. aerogenes and *gamma-Streptococcus*	1
Pseudomonas aeruginosa and *gamma-Streptococcus*	1
Subtotal	11
Infections with three species	
B. proteus, E. Coli, and *alpha-Streptococcus*	1
B. proteus, E. Coli, and *gamma-Streptococcus*	3
B. proteus, A. aeruginosa, and *alpha-Streptococcus*	1
B. proteus, A. aerogenes, and *gamma-Streptococcus*	4
Subtotal	9

TABLE 2
MINIMUM INHIBITORY CONCENTRATION OF MADRIBON FOR VARIOUS ORGANISMS

Organism	Number of strains inhibited Minimal inhibitory concentration, μg./ml.												
	1	2	4	8	16	32	64	125	250	500	1000	> 1000	Total
Gram-negative													
E. Coli					2	1	1					6	10
Coliform species												2	2
A. aerogenes												12	12
Proteus species					1	2	1	1		1	2	17	25
Pseudomonas aeruginosa												5	5
Gram-positive													
Alpha-Streptococcus					1	1							2
Beta-Streptococcus													
Gamma-Streptococcus					1	3	3	1	1	3	1	11	24
Staph. aureus	2			1				1	1	1	1	2	9
Staph. albus	1			1									2

by 1000 mg./ml. or less of Madribon; the remainder required significantly larger concentration of the drug for growth inhibition. Gram-negative strains showed more than 77 per cent of species relatively insensitive to Madribon. In this group only 40 per cent of *E. coli* and 20 per cent of *B. proteus* species were inhibited by the concentration of the drug—less than 500 mg./ml. The Gram-positive organisms were distinctly more sensitive to Madribon. The minimal inhibitory concentration for the majority of gamma-streptococci

TABLE 3
ANTIBACTERIAL EFFECT OF MADRIBON ON ORGANISMS IN THE URINE OF 59 PATIENTS

Organism	Number of species observed					
	Eradicated	Suppressed	Persistent	Emerged	Inadequate follow up	Total
Infections with single species						
E. Coli	1	1	1	—	—	3
Proteus species	1	2	4	2	—	9
Coliform species	—	1	—	—	1	2
A. aerogenes	—	1	3	—	1	5
Pseudomonas aeruginosa	—	—	2	—	—	2
Gamma-Streptococcus	4	1	3	3	2	13
Staph. aureus	5	1	1	2	1	10
Staph. albus	1	—	—	—	1	2
Subtotal	12	7	14	7	6	46
Infections with two species						
	—	10	8	—	4	22
Infections with three species						
	—	6	6	—	6	18
Total	12	23	28	7	16	86

(enterococci) and staphylococci did not exceed the concentration of 125 mg./ml. of Madribon.

Results

Antimicrobial effect of Madribon. TABLE 3 shows that the 39 single-species infections identified in the pretreatment cultures were comprised of 24 Gram-negative and 15 Gram-positive organisms. *E. coli* species were isolated in 3 and *Proteus* in 9 instances. *Aerobacter aerogenes* occurred in 5 cultures. Only 2 instances of *Pseudomonas aeruginosa* single infections were recorded. Two, or 8.9 per cent, of the 24 initially isolated Gram-negative species were eradicated after treatment. Another 20.8 per cent demonstrated at least tenfold reduction in the number of bacteria. The remaining 40 per cent of the species persisted throughout the study. None of the *Pseudomonas aeruginosa* responded

favorably to treatment. Similar results were observed in the majority of *Aerobacter* species. Thus, only a relatively small percentage of *E. coli* and *Proteus* species showed satisfactory results after Madribon treatment. The antibacterial effect upon Gram-positive organisms was more favorable, and a larger number of strains was eradicated or suppressed as a result of treatment, with 30.7 per cent of enterococci and 50 per cent of staphylococci eradicated from the urine of 15 patients. Another 8 to 10 per cent were markedly reduced

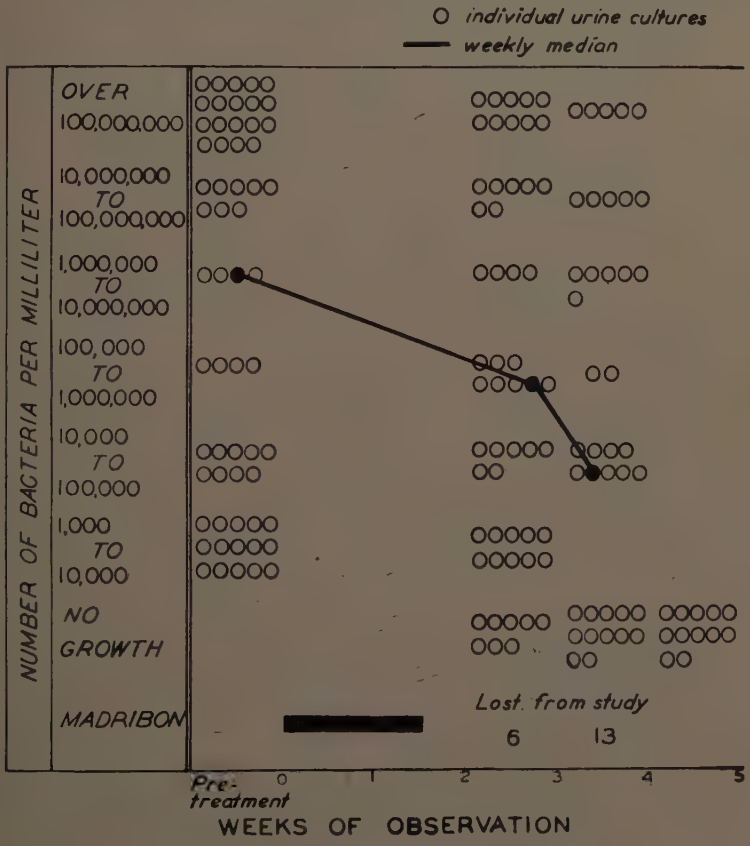


FIGURE 1. Antibacterial effect of Madribon.

in number in the posttreatment cultures. Only 16 per cent of Gram-positive strains emerged during and after the completion of treatment.

Generally poor results were obtained in the cases of mixed infections. None demonstrated bacterial eradication, although in 40 per cent a tenfold reduction of the bacterial population was noted. Considering the fact that one third of the mixed infections was incompletely followed and another third demonstrated persistence of bacteria, the over-all results were very unfavorable in this group of urinary infections.

The effect of Madribon on bacteriuria in 59 instances of urinary tract infections is illustrated in FIGURE 1. The pretreatment number of bacteria in the

promptly cultured urine, represented by open circles, ranged from a few thousand to 100 million bacteria per milliliter. The greatest number of bacteria was noticed in the range of 100 million and over with the median value, indicated by closed circles, of 1 to 10 millions of organisms per milliliter of urine. At the time of the first posttreatment cultures the urine became sterile in only 8 of the 53 samples examined. The median value dropped at the same time to the level of 100,000 to 1 million organisms per milliliter. A further drop in bacterial population with 4 additional sterile cultures was observed within the third and fourth weeks of the study. Patients with sterile urines were observed

TABLE 4
BACTERIOLOGICOCLINICAL EVALUATION OF MADRIBON

Type of infection	Kind of patient		Pretreatment cultures		Clinical response No. of patients				Bacteriological response No. of patients				Total patients
	Ward	Outpatient	Single organism	Multiple organism	Good	Fair	No response	Inadequate follow up	Good	Fair	No response	Inadequate follow up	
Acute cystitis	—	12	10	2	8	—	2[a]	2[a]	7	1	2[a]	2[a]	12
Cystitis and urethritis	—	14	11	3	5[a]	2[a]	3[a]	4	2	4[b]	4[a]	4	14
Cystitis, urethritis, and prostatitis	—	3	3	—	3	—	—	—	2	—	1	—	3
Postprostatectomy infection	16	3	9	10	1	8[d]	6[d]	4[b]	—	9[e]	6[e]	4[b]	19
Postoperative infection other than prostatectomy	4	2	4	2	—	2	3[a]	1[a]	—	—	5[a]	1[a]	6
Pyelonephritis, acute or chronic	—	1	1	—	1	—	—	—	1	—	—	—	1
	1	2	1	2	—	1[a]	2[a]	—	—	1[a]	2[a]	—	3
Chronic lower urinary tract infection	—	1	—	1	—	—	1	—	—	—	1	—	1
Total	21	38	39	20	18	13	17	11	12	15	21	11	59

[a] One patient with multiple organisms.
[b] Two patients with multiple organisms.
[c] Three patients with multiple organisms.
[d] Four patients with multiple organisms.
[e] Five patients with multiple organisms.

for another week, and their urine was found to be free of bacteria. This additional study of antimicrobial effect demonstrated clearly the trend of reduction in the number of bacteria in the urine and the relatively small percentage of sterile urines. It should be pointed out that the further reduction in the bacterial count in the second series of cultures was the result of a marked drop in the total number of patients lost from the follow-up at that time.

Clinical response to Madribon. The results of clinicobacteriological evaluation in 59 patients grouped in 8 various diagnostic categories are given in TABLE 4. The subjective clinical response as judged by the remission of symptoms, tolerance of drug, and restoration of satisfactory well-being is compared with the bacteriological response obtained *in vitro* and partially outlined in the above tables. In order to simplify the reading of results and give a more accurate

review of the over-all effect of Madribon in urinary tract infections, a uniform classification of both clinical and bacteriological responses was adopted. Thus, in the column of bacteriological response the previously used classifications of eradication and suppression are classified here as "good" and "fair" bacteriological responses, respectively.

The group of 29 patients with acute urinary tract infections such as cystitis, urethritis, and prostatitis were all observed in the outpatient department. Twenty-four demonstrated a single species, and the remaining 5 had mixed infections at the time of initial examination. A good clinical response was observed in 13, or 55 per cent, with complete clearance of bacteria. Two other patients obtained temporary remission of clinical symptoms and reduced their microbial number on follow-up cultures. In the group of fair bacteriological response, 3 additional patients were recorded despite the fact that clinically they became asymptomatic and classifiable with the group of good clinical response. Five clinical and 6 bacteriological failures were observed in this group.

Twenty-five patients with urinary infections associated with various surgical procedures, in the immediate and late postoperative course, exhibited a relatively higher incidence of clinical and bacteriological failures. Only 1 of the 25, or 4 per cent, responded favorably to Madribon therapy. Ten patients obtained fair clinical results and 9, or 36 per cent, failed to respond. The bacteriological results at the same time showed a higher incidence of failures and a total absence of available response.

One patient with acute pyelonephritis without demonstrable gross anatomical abnormality responded dramatically to Madribon. Of 3 patients with chronic pyelonephritis, 1 responded initially to the drug, but manifested a relapse of symptoms 2 to 3 weeks after completion of treatment. The remaining 2, who were found to have gross anatomical changes in the urinary tract did not respond to Madribon therapy.

One patient with chronic lower urinary tract infection had multiple perineal and scrotal fistulas, urethral strictures, and external urethrostomy. For three years he had been treated with all known antibiotics with very little effect; he also failed to respond to Madribon.

Of the 59 cases of urinary tract infection, favorable clinical results were obtained in 18, or 30.5 per cent, and favorable bacteriological results in 12, or 21 per cent. At the same time, 17, or 27.4 per cent, clinical and 21, or 35.5 per cent, bacteriological failures were recorded. Eleven cases were lost from adequate follow-up.

Table 5 shows the analysis of the clinical failures, the nature of the infection, and the complicating factors that were present. It is noteworthy that the highest incidence of failures occurred in the patients recuperating from various surgical urological procedures. A majority demonstrated mixed infections on pretreatment cultures insensitive to several antibiotics and chemotherapeutic agents. Approximately 70 per cent of the patients had some contributing factor responsible at least in part for the clinical failure.

Six clinical failures were observed in the patients with acute cystitis (simple or complicated by urethritis and prostatitis). Only two patients were found

TABLE 5
ANALYSIS OF CLINICAL FAILURES

Type of infection	No. of patients	Pretreatment cultures	Previous treatment	Complicating factor
Acute cystitis	2	*B. proteus*	Furadantin	—
		B. proteus *E. Coli* *gamma-Streptococcus*	Gantrisin Chloromycetin	—
Acute cystitis and urethritis	3	*B. proteus*	Chloromycetin Tetracycline	—
		A. aerogenes	Tetracycline	Urethral stricture
		B. proteus *E. Coli* *gamma-Streptococcus*	Resistant to all antibiotics	Urinary incontinence
Postprostatectomy infections	6	*B. proteus* *E. Coli*	Furadantin	Cystostomy tube *in situ*
		B. pyocyaneus *gamma-Streptococcus*	Chloromycetin Furadantin	—
		A. aerogenes *B. proteus*	Chloromycetin Tetracycline	—
		A. aerogenes	Tetracycline	Carcinoma of prostate
		A. aerogenes	Tetracycline Chloromycetin	—
		B. proteus *E. Coli*	Furadantin	Carcinoma of prostate, vesical calculus
Chronic lower urinary tract infection	1	*B. proteus* *E. Coli*	Chloromycetin Terramycin Achromycin	Perineal fistulas
Postoperative infections other than prostatectomy	3	*gamma-Streptoccocus*	Gantrisin Chloromycetin	Urethral strictures
		A. aerogenes	Tetracycline Achromycin	Cystostomy tube *in situ*
		B. proteus *Staph. albus*	Chloromycetin	Cystostomy tube *in situ*
Chronic pyelonephritis	2	*B. proteus*	Furadantin Gantrisin Chloromycetin	Nephrostomy and cutaneous ureterostomy
		B. proteus *Staph. albus*	Chloromycetin	Renal stone
Total	17			

to have some other complicating factor. All six exhibited resistance to other antimicrobial agents on previous treatment.

An anatomical alteration and stone formation in two instances of chronic pyelonephritis were contributing factors to their poor clinical response.

Pharmacological data on Madribon. Madribon was tolerated well by all 59 patients, with not even a mild rash occurring after administration of the total

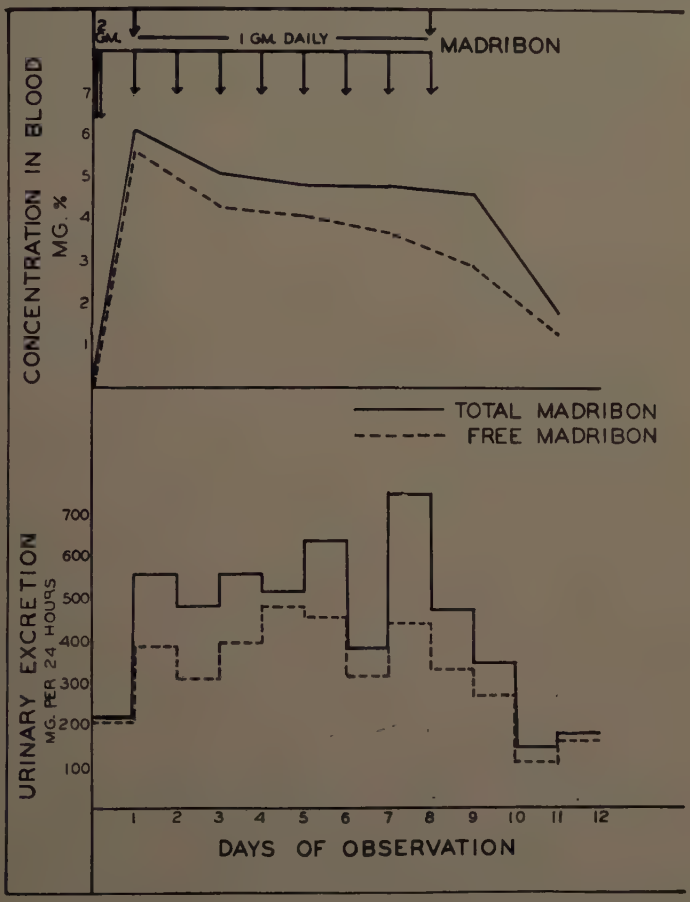


FIGURE 2. Average values of the concentration of Madribon in the blood and urine.

dose of 10 gm. of Madribon during a 9-day period. This was also true in patients with impaired renal function and evidence of nitrogen retention.

Blood levels and urinary excretion. Five patients were given the total of 10 gm. of Madribon in doses of 2 gm. the first day followed by 1 gm. for 8 successive days. Blood samples were taken 24 hours after the initial dose and every 48 hours thereafter. Urine was collected at 24-hour intervals during and after the treatment.

The average values of the concentration of Madribon in the blood and urine are recorded in FIGURE 2 and TABLE 6. The initial oral dose of 2 gm. raised

the concentration of free and total Madribon in the blood to 5.6 and 6.1 mg. per cent, respectively. On the subsequent daily dose of 1 gm., a plateau level of Madribon in the blood was observed, ranging between 3.7 and 4.3 mg. per cent for free Madribon and 4.6 and 5.1 for total Madribon. After the discontinuation of Madribon the plateau level of the total form of the drug persisted while the free Madribon dropped from 4 to 3 mg. per cent during the next 24 hours. After that there was a rapid decrease in concentration of free as well as total Madribon in the blood. At the end of 72 hours after the cessation of therapy the levels of free and total Madribon were recorded as 1.3 and 1.8, respectively. Two patients with evidence of impaired renal function were tested in the initial phase of our study and demonstrated 10 to 12 per cent higher blood levels after the administration of 1 or 2 gm. of Madribon. Urinary excretions were determined in the same patients placed on the standard dose

TABLE 6

AVERAGE BLOOD AND URINARY LEVELS AFTER INITIAL 2-GM. ORAL DOSE OF MADRIBON FOLLOWED BY DAILY DOSES OF 1 GM. FOR 8 DAYS*

Observation day	Blood levels, mg. %		Urinary levels, mg./24 hours	
	Free	Total	Free	Total
1	5.6	6.1	201	219
2			388	555
3	4.3	5.1	304	480
4			395	555
5	4.1	4.8	480	508
6			455	634
7	3.7	4.8	307	377
8			439	749
9	2.9	4.6	329	471
10			266	346
11	1.3	1.8	110	146
12			156	177

* Five patients.

of Madribon for a 9-day period. The average values of free Madribon obtained in the 24-hour urine tests ranged between 200 mg. after administration of 2 gm. of Madribon and 300 to 500 mg. while on a maintenance dose of 1 gm. daily. After the administration of the last dose of Madribon, 86 per cent of the ingested amounts was recovered in the 4 consecutive urine collections.

Discussion

The effect of the new sulfonamide Madribon has been tested under uniform conditions of treatment and observation in a variety of infections of the urinary tract. A detailed study of the microbial growth in the urine before and after treatment was employed in order to develop a better view of the behavior of pathogenic organisms under the effect of a tested drug. The widely utilized determinations of the degree of pyuria as criteria of progress or failure in the treatment of the infectious process had been found, in our previous experience, insufficiently accurate for adequate evaluation of any antimicrobial agent. On

the other hand, the quantitative enumeration of bacteria in the urine was connected with several problems that must be taken into consideration before a final opinion is formed. One fact that plays an important role in the detection of bacilluria is the method of obtaining a proper urinary specimen. It has been pointed out clearly by Kass[3] and others that bacterial multiplication in the urine is rapid and that bacterial counts rise to more than 10^8 per milliliter of urine within 8 to 12 hours after the inoculation of small numbers of bacteria. Our study[2] is in agreement with this observation, and we have found on many occasions enormously rapid multiplication of bacteria in urine retained in the bladder, especially in patients with incontinence, catheter drainages, or anatomical alteration of urinary outlet. Thus, the urine obtained from the residue, retained in the bladder for several hours, will yield a number of bacteria entirely different from that with urine obtained promptly. The second problem encountered in the quantitative estimation of bacteriuria is that of interpretation and transformation of results *in vitro* into substantial clinical data. A rather arbitrary classification was adopted in this and previous studies; namely, the minimum of a tenfold reduction of the number of bacteria in the urine obtained under standard conditions was considered a favorable response to antimicrobial agents. Other problems were elimination of possible contaminants from the urine, especially those with relatively high microbial count, and the presence of a Gram-positive organism in pretreatment urine cultures. On the basis of our experience with quantitative evaluation of cultures we disregarded cultures of Gram-positive species with lower counts than 10,000 and included those in which the Gram-positive species were persistent in numbers between 10,000 and 100,000 on repeated cultures and were associated with clinical symptoms.

The new sulfonamide has been of particular interest because its active form is excreted very slowly into the urine, yielding higher blood levels on relatively lower dosage, a property not observed in numerous older sulfonamides. Seventy-two hours after completion of therapy, 80 per cent of the drug was excreted in the urine at a concentration of 100 to 300 mg. per 24-hour urine samples. Koechlin *et al.*[5] found that the drug was excreted in the urine in conjugated form (a highly soluble glucuronide) and that its elimination is determined primarily by its conversion to the glucuronide. The acetylation is a relatively minor controlling factor in the excretion of Madribon in the urine. The high serum levels of the active form of Madribon (sufficient to have an antibacterial effect), the low dosage, prolonged excretion, and absence of untoward effects were found to be valuable assets in prolonged treatment of urinary infections.

The treatment of chronic urinary tract infections with antimicrobial drugs usually resulted in the eradication of the infection in a relatively small proportion of the patients, providing that the follow-up was sufficiently long and adequate. Bacteria are frequently present in the urine for some time after a given course of antimicrobial therapy, even in the absence of symptoms referable to the urinary tract. Thus, the continuous suppression of bacteriuria appears to be one of the important factors in controlling the infectious process of various types of urinary tract infections.

The clinicobacteriological data indicate that Madribon is a useful drug in some chronic and acute urinary tract infections. The low prevalence of favorable results and the small percentage of complete eradication of bacteria in the

urine were and are common observations in sulfonamide therapy of urinary tract infections. The analysis of our clinical failures shows that those infections that failed to respond to Madribon had also failed to clear with any other agents.

The effectiveness of Madribon therapy was better demonstrated in a quantitative study of bacteriuria. An abrupt and progressive decrease in the number of bacteria in cultured urines was a very striking effect of Madribon. The median number of bacteria dropped from several million to 100,000 at the end of the fourth week of observation.

The drug demonstrated activity against Gram-positive organisms and a few species of *E. coli* and *B. proteus*. Mixed infections generally responded poorly to Madribon treatment, although marked reduction in bacteriuria and eradication of sensitive organisms were observed. Madribon proved to be a very valuable adjuvant in the control of infections in patients maintained on catheter drainage.

Summary

The effectiveness of a new sulfonamide, Madribon, has been studied in a series of 59 patients. Favorable results were obtained in 30.5 per cent of the cases, a majority of them with Gram-positive species as the offending organism.

A tenfold reduction in bacterial count was observed in 25.5 per cent, and 27.4 per cent failed with Madribon treatment. It was found to be very effective against Gram-positive organisms, some species of *E. coli*, and *B. proteus*. Untoward reactions were not observed. The sulfonamide is excreted slowly in the urine, thus sustaining effective and prolonged levels of the drug in the blood.

Acknowledgments

We are indebted to Maude Browne for the illustrations and help in preparation of the manuscript, and to Paula Cohen for technical assistance in this investigation.

References

1. Bratton, A. C. & E. K. Marshall, Jr. 1939. A new coupling component for sulfanilamide determination. J. Biol. Chem. **128:** 537.
2. Draper, J. W. & M. Sierp. Unpublished data.
3. Kass, E. H. 1955. Chemotherapeutic and antibiotic drugs in the management of infections of the urinary tract. Am. J. Med. **18:** 764.
4. Knight, V., J. W. Draper, A. E. Brady & C. Attmore. 1952. Methenamine mandelate: antimicrobial activity, absorption and excretion. Antibiotics & Chemotherapy. **2:** 615.
5. Koechlin, B. A., W. Kern & R. Engelberg. 1959. A comparative study of the metabolism and urinary excretion of 2,4-dimethoxy-6-sulfanilamido-1,3-diazine (Madribon). Antibiotic Med. & Clin. Therapy. **6** (Suppl. 1) : 23.
6. Schnitzer, R. J., W. F. DeLorenzo, E. Grunberg & R. Russomanno. 1958. Chemotherapeutic studies with 2,4-dimethoxy-6-sulfanilamido-1,3-diazine (Madribon) (24370). Proc. Soc. Exptl. Biol. Med. **99:** 421.

SULFADIMETHOXINE IN URINARY TRACT INFECTIONS*

William S. Kiser, Otto C. Beyer, John D. Young
Division of Urology, Department of Surgery, University of Maryland School of Medicine, Baltimore, Md.

Infections of the urinary tract are among the most common seen in man, being exceeded only by those of the respiratory system.[1] A rational approach to therapy in these infections must begin with recognition of the causative microorganism and the conditions favoring its growth in the urinary tract.[2] Cook[3] emphasizes the importance of determining whether the therapeutic agent is being used to combat infection in an uncomplicated situation or in the presence of stone, tumor, or other obstructive factors contributing to urinary stasis.

According to Flippin and others[4, 5] 85 to 90 per cent of bacteria implicated in urinary infections are controllable with 1 or more members of the sulfonamide group. In addition to marked effectiveness against Gram-negative and Gram-positive primary invaders, sulfonamides offer ease of administration, an outstanding propensity for maintaining adequate therapeutic levels, a low percentage of complications, and relatively low cost.

In this study a new low-dosage long-acting sulfonamide, sulfadimethoxine, was evaluated in terms of effectiveness in controlling infections associated with a variety of urological disorders. The pharmacological properties of this sulfonamide that recommended its consideration were low-dose effectiveness and long-acting potential. Brandman *et al.*[6] have demonstrated therapeutic plasma levels (6 mg. per cent) 4 hours after oral administration of 1 gm., with therapeutically active blood levels maintained 24 hours or more.

Material and Methods

One hundred eighty-five patients from the urology clinic and inpatient urology service of the University Hospital received sulfadimethoxine for urinary tract infections. Treatment was prescribed for uncomplicated urinary infections, for infections complicated by the presence of stasis secondary to obstruction in the urinary tract, and for prophylaxis following surgical intervention or urologic instrumentation for diagnostic or therapeutic purposes. The ages of those treated varied from 3 to 87 years, with 40 per cent of the cases 55 years of age or older. Duration of therapy varied from 2 weeks to 4 months for an average of 3 weeks. The dosage prescribed for acute or persistent infections and following surgery was 0.5 gm. every 12 hours. When prophylaxis was indicated following instrumentation or during prolonged catheter drainage, 0.5 gm. daily was used. Urine cultures, urinalyses, leukocyte counts, and hemoglobin determination were obtained prior to onset and upon completion of treatment in acute infections or at frequent intervals in those under long-term care.

* The study reported in this article was supported by a grant from Hoffmann-La Roche Inc., Nutley, N. J.

Results

Sulfadimethoxine therapeutically. One hundred fifty-eight patients with acute or chronic urinary tract infections were treated with sulfadimethoxine (TABLE 1).

Therapeutic effectiveness was evaluated in both uncomplicated infections and in those complicated by the presence of calculi, tumor, cicatricial changes, or other obstruction. In over-all analysis, 78 per cent of the patients were rated as good to excellent in their clinical response. A comparison of cases with acute and chronic infections revealed comparable clinical responses as regards symptomatic improvement. However, bacterial resistance and emergence of new organisms during therapy were significantly greater in chronic

TABLE 1
EVALUATION OF PATIENT RESPONSE

Condition	No. of cases	Response*			
		Excellent	Good	Fair	Poor
Pyelonephritis					
Acute	13	5	3	1	4
Chronic	11	1	6	4	0
Cystitis					
Acute	14	4	8	1	1
Chronic	37	2	27	4	4
Urethritis					
Acute	5	0	5	0	0
Chronic	38	2	30	6	0
Epididymitis					
Acute	10	2	4	3	1
Prostatitis					
Acute	6	2	4	0	0
Chronic	24	0	19	5	0
Total	158	18	106	24	10

* Standards: excellent—symptoms relieved, urine became sterile and microscopically negative; good—symptoms improved, urine may have become sterile and microscopically negative; fair—no exacerbation of symptoms and no progress of disease; poor—required additional therapeutic measures.

infections. Infections of the lower urinary tract showed an over-all response 10 per cent better than kidney infections. No significant difference was noted in the clinical response of complicated and uncomplicated infections of the lower urinary tract. Uncomplicated infections of the upper urinary tract showed a response to therapy 15 per cent better than did those complicated by one of the above factors.

Sulfadimethoxine prophylactically. The prophylactic use of antibacterial drugs following urologic surgery and instrumentation currently is being advocated by many investigators. One hundred fifty patients in the series received sulfadimethoxine prophylactically. Forty underwent open urologic surgery and 27 endoscopic surgery (TABLE 2). In extensive surgical procedures sulfadimethoxine was administered together with a wide-spectrum antibiotic for 3 to 5 days postoperatively, then continued alone for 2 or more weeks. In

90 per cent of urologic surgery cases, sulfadimethoxine demonstrated a good prophylactic effect; that is, there was no evidence of superinfections or exacerbation of symptoms in resistant infections. Urologic instrumentation for diagnostic evaluation or for therapeutic purposes was performed in 133 patients. Sulfadimethoxine provided effective prophylaxis in 97 per cent of these cases. In 36 patients with indwelling catheter drainage exceeding 2 weeks' duration, only 2 cases demonstrated clinical evidence of infection that necessitated further therapeutic measures. In 55 patients undergoing urethral dilatations at

TABLE 2
EFFECTIVENESS OF SULFADIMETHOXINE USED PROPHYLACTICALLY

Condition	No. of cases	Effectiveness* (per cent)
Open surgery		
Kidney	4	
Ureter	4	
Bladder	9	90
Prostate	12	
Scrotal	6	
Perineal	5	
Endoscopic surgery		
Transurethral resection	22	
Resection of bladder lesion	3	89
Extraction of ureteral stones	2	
Instrumentation		
Ureteral catheterization	15	
Serial urethral dilatations	55	97
Cystoscopy	27	
Prolonged urethral catheter drainage (2–14 weeks)	36	

* Effective prophylaxis: no evidence of superinfection or exacerbation of symptoms in resistant infections.

periodic intervals for chronic female urethritis or urethral strictures, uniformly good results were noted.

Bacterial studies. The antibacterial effectiveness of sulfadimethoxine in 75 cases was studied by urine cultures before and after treatment. Of 105 organisms identified, 75 per cent were Gram-negative and 25 per cent Gram-positive pathogens. Mixed infections were present initially in 11 per cent of cases. The most common organisms, constituting 87 per cent of the total, were *Escherichia coli* (37 per cent), *Aerobacter aerogenes* (17 per cent), *Staphylococcus albus* (14 per cent), *Bacillus proteus* (14 per cent), and *Pseudomonas aeruginosa* (9 per cent). Those occurring less frequently were *Staphylococcus aureus*, *Streptococcus viridans*, and *Enterococcus* (TABLE 3).

After treatment with sulfadimethoxine, sterile urine was present in 27 per cent of cases with Gram-negative organisms and 56 per cent of cases with Gram-

positive organisms. The drug demonstrated marked effectiveness against the organisms found most commonly in urinary infections; that is, *E. coli*, *A. aerogenes*, and *S. albus*. Sterile urines were obtained in 10 per cent or less of cases infected with *B. proteus* and *Ps. aeruginosa*.

In 48 cases (57 per cent) the organisms originally present were cultured from the urine following treatment. Resistant organisms persisted with equal incidence whether the patient received 0.5 gm. or 1 gm. daily. In 20 cases (23 per cent) a new bacterial strain emerged during treatment, usually in cases with therapy of long duration (60 per cent were treated for 3 weeks or more). There appeared to be a significant inverse correlation between dosage of drug and emergence of new bacterial strains, the latter occurring twice as frequently on a daily dosage of 0.5 gm., as compared with 1 gm. of sulfadimethoxine daily. Cases showing resistant bacteria or emergence of new strains were evaluated as to clinical response. Of these cases 81.2 per cent demonstrated a good symptomatic response to therapy in spite of persistent bacteria in urine.

TABLE 3
SUMMARY OF ORGANISMS CULTURED FROM URINE

Organism	No. times isolated	Organism eradicated	Organism persisted	Emergence of new strain
E. coli	38	11	23	4
Aerobacter aerogenes	18	10	4	4
Proteus vulgaris	15	1	11	3
Ps. aeruginosa	9	1	3	5
Staph. albus	14	7	5	2
Staph. aureus	3	3	0	0
Enterococcus	5	2	1	2
Strep. viridans	3	2	1	0
Total	105	37	48	20

Twenty-two cases (38 per cent) with sulfonamide-resistant Gram-negative organisms received wide-spectrum antibiotic therapy (chloramphenicol, tetracycline, penicillin, streptomycin, or Furadantin) specifically selected on the basis of disk-sensitivity tests. Eighty-two per cent of sulfonamide-resistant organisms were also resistant to wide-spectrum antibiotics, as shown by after-treatment cultures.

In this study, clinical effectiveness of the drug could not be correlated with bacterial sensitivity using high-concentration sulfadimethoxine discs on various media. This procedure was abandoned after 75 consecutive cases failed to demonstrate an accurate correlation.

Discussion

As Salvaris[1] has aptly pointed out, it is common knowledge that many urinary infections are self-limiting and will clear with no drug therapy, making assessment of the potency or efficacy of a drug no easy matter. In evaluating acute and chronic infections in this series of patients, clinical response in terms of symptomatic improvement appeared to be essentially the same, with an

over-all good to excellent result in 78 per cent of cases. Bacterial resistance and emergence of new organisms were observed 90 per cent more frequently in infections requiring long-term therapy. Sulfadimethoxine may have contributed to creation of bacterial resistance in a portion of these cases. However, it is felt that a significant number of resistant strains resulted from cross infection with antibiotic-resistant strains derived from the hospital environment and introduced by instrumentation. This coincides with observations of other investigators.[7] The symptomatic clinical response was significantly better in uncomplicated infections of the upper urinary tract than in those with underlying pathology causing urinary stasis. Infections of the lower urinary tract showed essentially the same clinical response, from the standpoint of symptomatology, whether or not the process was complicated. However, the incidence of eradication of the pathogenic organism was 88 per cent greater in uncomplicated infections of the lower tract than in complicated ones.

The administration of antibacterial therapy following urologic procedures for prophylaxis has been questioned by some investigators. Recent studies, on the other hand, point to definite indications for the use of prophylactic medication. Cordonnier,[8] in performing urethral dilatations, advocates sulfonamides to complete therapy. Davis[9] recently has shown significantly decreased incidence of infection following instrumentation in patients administered prophylactic sulfonamide therapy as compared with a control group receiving placebos. Our study showed uniformly good results in a large group of patients who received sulfadimethoxine for prophylactic purposes. Repeated instrumentation was necessitated in many instances, often in the presence of infected urine, and the absence of adverse effects in essentially all cases is believed to demonstrate the prophylactic efficacy of sulfadimethoxine.

Four patients (an incidence of 2.1 per cent) experienced side effects believed to be due to sulfadimethoxine therapy. One patient developed severe generalized urticarial rash; 2, minor urticarial rashes; and 1, headache and dizziness during therapy. All symptoms developed within the first 3 days of therapy and disappeared after the drug was discontinued. No secondary anemia or leukopenia was observed in 65 cases in which serial hemoglobin determinations and leukocyte counts were performed. There was no evidence of crystalluria in more than 150 cases in which repeated urinalyses were obtained.

Clinical improvement could be correlated with dosage of sulfadimethoxine in certain cases. Symptoms were relieved and the urine became sterile in several cases after the dosage was increased from 0.5 gm. daily to 0.5 gm. every 12 hours. It is felt that, in the treatment of acute or persistent urinary infections and as prophylaxis following instrumentation in the presence of infection or after surgery, the dosage should be 2 gm. initially and 0.5 gm. every 12 hours. In uncomplicated instrumentations or with prolonged catheter drainage, 0.5 gm. daily should suffice.

Conclusions

One hundred eighty-five patients with a variety of urologic conditions were treated with a new low-dosage, long-acting sulfonamide, sulfadimethoxine.

Good to excellent clinical response was noted in 78 per cent of patients dur-

ing treatment of urinary infections. Results were generally better in acute uncomplicated infections.

As a prophylactic agent, sulfadimethoxine demonstrated greater than 90 per cent effectiveness, following surgical procedures or urologic instrumentation.

Common urinary pathogens showed marked sensitivity to this sulfonamide, with sterile urine after treatment in 30 per cent Gram-negative and 56 per cent Gram-positive organisms.

A good clinical response was obtained in 81 per cent of cases, with persistent bacteria in the urine after treatment.

Low toxicity was demonstrated, with 2.1 per cent incidence of side effects. No evidence of leukopenia, secondary anemia, or crystalluria following prolonged therapy was demonstrated in this series.

Recommended dosage of sulfadimethoxine in the treatment of urinary tract infections is 2.0 gm. as initial dose and 0.5 gm. every 12 hours.

References

1. Salvaris, M. 1958. Treatment of urinary infections with nitro-furantoin. Brit. J. Urol. **30**(3): 303.
2. Rhoads, P. S., C. E. Billings & V. J. O'Connor. 1952. Antibacterial management of urinary tract infections. J. Am. Med. Assoc. **148**(3): 165.
3. Cook, E. N. 1955. The management of infections of the urinary tract. Ann. Intern. Med. **43**: 316.
4. Flippin, H. F. 1955. The evolution of water casting. J. Urol. **74**(5): 660.
5. Yow, E. H. 1955. A re-evaluation of sulfonamide therapy. Ann. Intern. Med. **43**: 323.
6. Brandman, O., C. Oyer & R. Engleberg. 1959. Blood levels and urinary excretion of a long-acting sulfonamide, Madribon in man. J. Med. Soc. New Jersey. **56**: 24.
7. Miller, A., W. A. Gillespie, K. B. Winton, N. Slade & J. P. Mitchell. 1958. Postoperative infection in urology. Lancet. **2**: 608.
8. Cordonnier, J. J. 1955. Urethritis in the female. Postgrad. Med. **18**(3): 155.
9. Davis, J. H. & L. Persky. 1959. An evaluation of post-catheterization prophylactic chemotherapy. Am. Urol. Assoc. Ann. Meeting, April 21, 1959. To be published.

Discussion

Grayson Carroll (*St. Louis University School of Medicine, St. Louis, Mo.*): Any clinical study is difficult to evaluate because of the many variables, but in the two excellent papers by Sierp and Draper and Kiser and his co-workers on the clinical effectiveness of sulfadimethoxine in urology, the authors have taken these factors into consideration in their conclusions. They have analyzed the data with respect to whether infections were acute or chronic, in the upper or lower urinary tract, and obstructive or nonobstructive; whether therapy was pre- or postoperative; whether patients were ambulatory or hospital; and whether instrumental manipulation or catheter drainage was required. The infecting organisms were evaluated as resistant or nonresistant types and the number of cases studied was adequate. With respect to adequacy of number, I found, in a study of other drug therapy, that the analysis of 1000 cases gave a result no different from that obtained with 500 cases. However, there was some change in the percentages obtained in 100 cases as contrasted with those found with 500—especially in the case of less frequently occurring organisms.

The two studies are similar in that, in general, the same dosage was used

and the methods of investigation were similar—urinalyses, cultures, clinical symptoms, and the noting of untoward effects. However, the types of patients studied were quite different, and therefore the classifications were different.

Sierp and Draper classified the result as "good" if, after 4 weeks after discontinuing treatment, the patient remained asymptomatic, the urine was microscopically negative, and 2 urine cultures were sterile. This is a rigid criterion.

In addition, the 59 patients studied were men, the majority of whom had prolonged catheter drainage for urinary incontinence or obstructive prostatic conditions, urethral stricture, and chronic renal disorders. The majority of these cases had been treated unsuccessfully with other antimicrobial agents, indicating a high percentage of organisms resistant to other drugs. The results obtained must be interpreted in this light. This may also account for the persistence of 40 per cent of the Gram-negative organisms throughout the treatment.

The fact that only 16 per cent of the Gram-positive organisms survived the sulfadimethoxine treatment indicates that it is most effective in the coccal infections, many of which were resistant to other antibiotics.

The blood level studies correspond with previously published investigations, indicating that 0.5 gm. daily is normally an adequate dose for maintaining satisfactory blood levels.

The study by Kiser and his co-workers involved a different category of patients, some uncomplicated cases, some with secondary stasis, and some treated prophylactically before instrumentation.

In this over-all analysis, 78 per cent of cases were rated as "good to excellent" in their clinical response. Sterile urine was present in 27 per cent of cases with Gram-negative organisms and in 56 per cent of cases with Gram-positive organisms. This again demonstrates that the greatest value of the drug lies in treatment of the patient harboring the Gram-positive organisms.

Both studies indicate a poor effect in the patients with *Pseudomonas* organisms, which corresponds to our observations. I would like to see further clinical studies of the effect on the *Proteus* and *Aerobacter* organisms. The analysis of the studies discussed in this paper leaves me a bit confused as to the effectiveness of the drug against these organisms. Kiser's group finds it effective in 10 per cent or less of the *Proteus* and *Pseudomonas* cases, and Draper's group found it of limited effectiveness in *Aerobacter* and *Proteus*. The limited number of patients infected with these organisms makes the results inconclusive. The effect on *Aerobacter* is important because, in a recent study presented to the American Genitourinary Surgeons, Lattimer demonstrated the high incidence of resistant *A. aerogenes* in recent years.

Kiser and his associates noted the development of resistant strains during sulfadimethoxine treatment, which is usual with many drugs, but especially so with sulfonamides. To pinpoint clinically the fact that the organisms have developed resistance is difficult, since often they are merely the survivors of resistant strains already present.

The favorable result obtained prophylactically with sulfadimethoxine coincides with my observations and may be used to good advantage. The observa-

tion that new strains of bacteria appear more frequently on the smaller dosage (0.5 gm.) as compared with the 1-gm. dosage may be important clinically and justifies increased dosage or a booster dose every 2 or 3 days.

Kiser's group noted that 22 of the cases that had sulfa-resistant organisms had been treated with other drugs and that these were 82 per cent resistant. This points up the fact that many of the urinary infections we now treat have been exposed to antibiotics, and that a high percentage is resistant. It is no wonder then that any drug studied these days shows far less than 100 per cent effectiveness.

It is also reported that "clinical effectiveness of the drug could not be correlated with bacterial sensitivity using high-concentration sulfadimethoxine disks on various media. This procedure was abandoned after 75 consecutive cases failed to demonstrate an accurate correlation." This deserves thorough discussion. William A. Leff, in a study on paraplegic patients at the Kessler Institute, St. Barnabas Medical Center, Newark, N. J., also stated: "There was no relationship between the clinical effectiveness of sulfadimethoxine and the *in vitro* sensitivity." B. Fust of Basle, Switzerland, also found variation between the *in vitro* and animal studies. The sensitivity tests as performed by the disk method in St. John's Hospital, St. Louis, Mo., also fail as an index of the effectiveness of sulfadimethoxine in patients. Although the sensitivity tests showed no inhibition in the laboratory, the drug was effective clinically. B. H. Leming, at the University of Tennessee, Knoxville, Tenn., in an exhaustive study reported in this monograph demonstrated without question that the *in vitro* sensitivity tests are no indication of the clinical usefulness of the drug. This is one of the most important observations in this monograph and it should be widely publicized in view of the fact that sensitivity tests have proved to be very reliable in regard to antibiotics. Until the laboratory develops a more satisfactory method of determining the sensitivity for the sulfa drugs, we must rely on the identification of the organism and the manner of behavior of the disease to determine when the sulfa drug should be given.

I have observed the sulfa drug in the prostate of the dog and man after its administration by mouth. The concentration in the dog averaged 1.8 mg. and in the human, 5.23 mg., which should be sufficient to cause bacteriostasis. The clinical results in man seem to corroborate this. Of 18 men treated for prostatitis, all of whom showed microscopically a positive culture and pus in the prostate secretion, 12 were culturally negative after 6 weeks of treatment with 1 gm. of sulfadimethoxine daily and massage of the prostate weekly.

Ironson and Patel, of the University Hospital of Iowa, Iowa City, Iowa, recovered 0.44 per cent of sulfa drug in the tissue of a prostate gland that was removed. This is a somewhat different method of determining the presence of sulfonamides in the prostate, and they state "that an investigation of these sulfonamide levels in different tissues might well uncover a more specific method of treatment."

We are satisfied that prolonged administration of sulfadimethoxine in cases of cystitis and chronic pyelonephritis where no demonstrable obstruction is present is well indicated.

It would appear, then, that when sulfadimethoxine is administered in specifically selected cases, it is quite a valuable addition to our sulfonamide armamentarium. The reports would indicate that it is most useful where there are present Gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus hemolyticus*, and Gram-negative bacilli such as *Escherichia coli* and, in some instances, *Aerobacter aerogenes* and *Proteus vulgaris*.

EXPERIMENTAL APPROACH TO TOPICAL ANTIBACTERIAL THERAPY

E. Grunberg and R. J. Schnitzer
Department of Chemotherapy, Hoffmann-La Roche Inc., Nutley, N. J.

Research to find substances effective as topical antibacterial agents is not a new field of endeavor. Interest in this area has, moreover, increased in recent years since the bacterial strains most commonly causing primary and secondary superficial infections have shown a steady increase in resistance to modern-day chemotherapeutic agents.[1-4]

The majority of laboratory techniques used for estimating the potency of antibacterial agents have been *in vitro* tests.[5] Although it is not our intention to belittle such tests, which in recent years have led to the discovery of clinically useful topical agents, the validity of *in vitro* tests for the chemotherapy of infectious diseases has always been questionable.

When the search for chemical agents acting on pathogenic microorganisms began, investigators were confronted by the following interesting phenomena. (1) Compounds of high activity *in vitro* were completely inactive *in vivo*. Examples of this lack of correlation are the disappointing results that Robert Koch and Emil von Behring obtained when they tried to influence the diphtheria infection of guinea pigs with phenol or mercuric chloride, the best-known disinfectants of that time, and Koch's unsuccessful attempts to use aurothiocyanate, a powerful *in vitro* agent, against tuberculosis in guinea pigs.[6] (2) Compounds of high activity *in vivo* have little or no activity *in vitro*. Although there is a large number of compounds of different chemical composition that fall into this category, well-known examples of this are the arsonic acids and arsenobenzenes which are active *in vitro* only in their oxidized forms as arsenoso compounds. Among the antibacterial drugs that belong in this group are the sulfonamides, which exert their effect predominantly *in vivo* while the activity *in vitro* can be demonstrated only under special conditions and in media in which the presence of inhibitory substances is carefully avoided.[7]

An example that encompasses both of the above-mentioned phenomena is the observation by Morgenroth *et al.*[8] that high *in vitro* activity in a series of acridine derivatives was represented by little or no local activity *in vivo*, and vice versa.

It is apparent, of course, that in many instances, particularly in the case of modern antibiotics such as penicillin and streptomycin, activity *in vitro* can be used as a lead for activity *in vivo*. However, no concrete evidence seems available that the activities *in vitro* and *in vivo* are due to the same mechanism. This fact is not surprising because the biological conditions that prevail in the infected tissues, the sensitive equilibrium of the natural defense mechanism of the host, and the invasiveness of the organism are much more complicated than the conditions that exist in an *in vitro* test even though it may not be true, necessarily, that the latter test is based on a biologically simple system.

Therefore, the problem for the experimental approach to topical antibacterial therapy is to find a satisfactory test by which the reaction of the infecting organism to a chemical agent can be studied in the presence of tissues. It must be a technique adapted to the facilities of the average laboratory and sufficiently

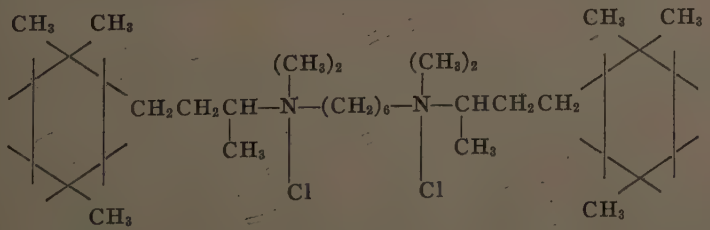
reliable to allow the evaluation of large numbers of compounds in adequate numbers of animals. From these limitations it is obvious that a relatively small laboratory animal must be employed. In consideration of these facts, the method of the local subcutaneous infection of mice as originally employed by Morgenroth and Abraham[9-11] has been selected for testing the topical effect of chemotherapeutic agents. It is obvious that under the conditions of such an experiment an unnatural infection is being studied but, as may be recalled, the history of chemotherapy shows that the major progress has been based on the use of such *in vivo* testing techniques.

Method

Practically all pathogenic cocci as well as a number of other organisms (for example, *Corynebacterium diphtheriae*, numerous members of the *C. pseudodiphtheriae* group, *Escherichia coli*, and other Gram-negative bacteria[12]) form very characteristic local lesions if injected into the subcutaneous tissue of the abdominal wall of mice. The early stage of acute inflammation is followed by a chronic purulent stage during which the causative organisms can be recovered. Depending on the organism used and the dose of infection employed in individual cases, the subcutaneous focus may perforate the skin in the later stages of infection.

The standard method used for the screening of compounds for demonstration of topical antibacterial activity consisted, therefore, of the subcutaneous injection into the center of the abdominal wall of the desired dilution of the bacterial culture (that is, *Streptococcus hemolyticus* and *Staphylococcus aureus*, 0.2 ml. of a 0.4×10^{-1} dilution; *E. coli*, 0.5 ml. of a 1.0×10^{-1} dilution) followed by immediate infiltration of the same area by 1.0 ml. of graded concentrations of the compound to be tested. Twenty to 24 hours later the animals were sacrificed and cultures taken from the site of infection and treatment. A count of 10 colonies or less was considered to be the end point of activity and on the basis of these observations the 50% curative dose was calculated according to the method of Reed and Muench.[13] In all experiments control animals showed heavy growth on culture.

Included among the drugs tested are such well-known topical antibacterials as nitrofurazone (Furacin), polymyxin B sulfate, neomycin sulfate, bacitracin, and penicillin, as well as a new agent triclobisonium chloride (Triburon chloride*)[12] whose chemical formula is N,N′-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N′-dimethyl-1,6-hexanediamine bis(methochloride).†



* Product of Hoffmann-La Roche Inc., Nutley, N. J.
† Synthesized by S. Teitel and M. W. Goldberg.

Experimental Results

The data on the activity of the single local administration of Triburon against the subcutaneous bacterial infection of mice can be evaluated on the basis of two criteria: (1) the amount (calculated for the CD_{50}) necessary to influence the infection, and (2) the number of strains that responded to the agent under test.

TABLE 1 presents the results on the activity of the 6 test agents against the local infection of mice with 5 strains of *Str. pyogenes*. Sensitivity of all strains was observed only in 2 cases. These 2 agents were triclobisonium chloride and

TABLE 1

ACTIVITY OF TRICLOBISONIUM CHLORIDE, NEOMYCIN SULFATE, PENICILLIN, BACITRACIN, POLYMYXIN B SULFATE, AND NITROFURAZONE IN THE LOCAL SUBCUTANEOUS INFECTION OF MICE WITH *STR. PYOGENES*

Drug	No. of strains tested	No. of strains sensitive	Average CD_{50}* μg./ml.
Triclobisonium	5	5	4.6
Neomycin	5	5	49.6
Penicillin	5	4	1.7
Bacitracin	5	4	57.5
Polymyxin B	5	4	124.9
Nitrofurazone	5	4	129.4

* Calculated only on sensitive strains.

TABLE 2

ACTIVITY OF TRICLOBISONIUM CHLORIDE, NEOMYCIN SULFATE, POLYMYXIN B SULFATE, BACITRACIN, PENICILLIN, AND NITROFURAZONE IN THE LOCAL SUBCUTANEOUS INFECTION OF MICE WITH *STAPH. AUREUS*

Drug	No. of strains tested	No. of strains sensitive	Average CD_{50}* μg./ml.
Triclobisonium	7	7	6.2
Neomycin	7	7	6.3
Polymyxin B	7	7	189.9
Bacitracin	7	5	657.3
Penicillin	7	2	90.0
Nitrofurazone	7	1	1000.0

* Calculated only on sensitive strains.

neomycin sulfate. Triclobisonium chloride, however, was approximately 11 times more active than the antibiotic. With the remaining 4 agents, 1 strain in each case did not respond to therapy.

As might be expected with streptococci, the strains which responded to penicillin were highly sensitive. The activity of bacitracin was on the order of that of neomycin sulfate, while polymyxin B sulfate and nitrofurazone were less active than the latter.

Somewhat different results were seen in the experiments with 7 strains of *Staph. aureus* (TABLE 2). All strains were susceptible to triclobisonium chloride, neomycin sulfate, and polymyxin B sulfate. Triclobisonium chloride and neomycin sulfate were of the same order of activity. Polymyxin B sulfate was

about 30 times less active than these 2 agents. Five of the 7 strains responded to bacitracin. The CD_{50} of the latter antibiotic, although calculated only on the basis of sensitive strains, was, even under these conditions, approximately 104 times less active than triclobisonium chloride. Since, of the 7 strains, response to nitrofurazone and penicillin occurred in 1 and 2 strains respectively, no valid comparison of average response can be made with the other agents.

In the case of *E. coli*, 11 strains were tested. From the results given in TABLE 3 it may be seen that polymyxin B sulfate and neomycin sulfate were effective against all strains tested, with the former being 8 times more effective than the latter. Nine and 6 strains responded to nitrofurazone and triclobisonium chloride, respectively. The response of the sensitive strains to the latter 2 substances was approximately equal. Only 2 strains responded to bacitracin at the maximum dose tested.

The data in these tables, therefore, show that consistent activity was present with triclobisonium chloride and neomycin sulfate against the local streptococ-

TABLE 3

ACTIVITY OF POLYMYXIN B SULFATE, NEOMYCIN SULFATE, NITROFURAZONE, TRICLOBISONIUM CHLORIDE, AND BACITRACIN IN THE LOCAL SUBCUTANEOUS INFECTION OF MICE WITH *E. COLI*

Drug	No. of strains tested	No. of strains sensitive	Average CD_{50}* μg./ml.
Polymyxin B	11	11	7.0
Neomycin	11	11	58.4
Nitrofurazone	11	9	303.1
Triclobisonium	11	6	373.1
Bacitracin	11	2	5000.0

* Calculated only on sensitive strains.

cal and staphylococcal infections of mice. Triclobisonium chloride was superior to neomycin sulfate in the streptococcal infection, and of equal activity against staphylococci. Polymyxin B sulfate was consistently active against staphylococci and *E. coli*. In staphylococci it was, however, much less effective than triclobisonium chloride and neomycin sulfate. It was the most potent agent against *E. coli*. Although neomycin sulfate was effective against all strains of *E. coli* tested, it was appreciably less active than polymyxin B sulfate.

Discussion

It may appear unsuitable to evaluate compounds meant for surface application by a method that plants the causative organisms into tissue spaces, thus making not only the infection itself but even its localization different from practical conditions, but it was felt that it was permissible to use the technique for various reasons. Although in both *in vitro* and local *in vivo* tests there is direct contact between drug and microorganism, there is no evidence that the activity in the tissue spaces imitates the conditions of the *in vitro* test. Infected surfaces are living tissue subject to its specific reaction. It is well known that even on the infected skin a considerable excess of a chemotherapeutic agent over

that indicated by an *in vitro* test is required to overcome the competitive inhibition of live tissue and exudate. These considerations, therefore, would seem to make it desirable to have an *in vivo* screening method for evaluating the possible topical activity of chemotherapeutic agents. The subcutaneous infection of mice as described in this paper is such a procedure.

As to the practical value of the test in mice as a selecting method for clinical application of topical antibacterial agents, it is somewhat impressive that excellent results were obtained with such compounds as neomycin sulfate and polymyxin B sulfate, the clinical value of which is very well known.

Triclobisonium chloride, which in this screening test would seem to be a potent agent for topical antibacterial therapy, has recently been reported as such.[14, 15]

Summary

(1) The method of the local subcutaneous infection of mice as originally described by Morgenroth and Abraham is recommended as a procedure for the selection of topical antibacterial agents.

(2) By use of this method, well-known topical antibacterials such as nitrofurazone, polymyxin B sulfate, neomycin sulfate, bacitracin, and penicillin as well as a new agent, triclobisonium chloride, show an effect to a greater or lesser degree against strains of *Str. pyogenes*, *Staph. aureus*, and *E. coli*.

References

1. Barber, M. & C. C. Dutton. 1958. Antibiotic-resistant staphylococcal outbreaks in a medical and a surgical ward. Lancet. **2:** 64–68.
2. Koch, M. L., D. Lepley, Jr., C. M. Schroeder & M. B. Smith. 1959. Study of staphylococcic infections occurring on a surgical service. J. Am. Med. Assoc. **169:** 99–105.
3. Waisbren, B. A. & C. L. Strelitzer. 1958. A five year study of the antibiotic sensitivities and cross resistances of staphylococci in a general hospital. Antibiotics Ann. 1957–1958. : 350–364.
4. Neomycin: Its Nature and Practical Application: 1958. : 219. S. A. Waksman, Ed. Williams & Wilkins. Baltimore, Md.
5. Antiseptics, Disinfectants, Fungicides, and Chemical and Physical Sterilization. 1954. G. F. Reddish, Ed. Lea & Febiger. Philadelphia, Pa.
6. Koch, R. 1881. Ueber Desinfection. Mitteil. Kais. Gesundh. **1:** 234–282.
7. Henry, R. J. 1944. The Mode of Action of Sulfonamides. Josiah Macy, Jr. Foundation. New York, N. Y.
8. Morgenroth, J., R. Schnitzer & E. Rosenberg. 1921. Ueber chemotherapeutische Antisepsis. III Mitteilung. Ueber ein neues Antiseptikum (2-Aethoxy-6,9-diaminoakkridinchlorhydrat.). Deut. med. Wochschr. **44:** 1317.
9. Morgenroth, J. & L. Abraham. 1920. Ueber chemotherapeutische Antisepsis. Deut. med. Wochschr. **46:** 57–60.
10. Schnitzer, R. J. 1928. Handbuch der Biologischen Arbeitsmethoden. E. Abderhalden, Ed. Urban und Schwartzenberg. Berlin, Germany.
11. Grunberg, E., R. J. Schnitzer & C. Unger. 1948. Mechanism of the topical effect of penicillin G in experimental local streptococcal infections. Yale J. Biol. Med. **20:** 479–486.
12. Schnitzer, R. J., E. Grunberg, W. F. DeLorenzo & R. E. Bagdon. 1959. Triburon, an antibacterial agent with local activity in living host tissues. Antibiotics & Chemotherapy. **9:** 267–276.
13. Reed, L. J. & H. Muench. 1938. A simple method of estimating fifty per cent endpoints. Am. J. Hyg. **27:** 493–497.
14. Edelson, E., E. Grunberg & T. V. Morton. 1959. Clinical appraisal of a new topical quaternary compound Ro 5-0810/1. Antibiotics Ann. 1958–1959. : 110–112.
15. Robinson, R. C. V. & L. E. Harmon. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. : 113–114.

EVALUATION OF TRIBURON* ALONE AND WITH HYDROCORTISONE FOR TOPICAL THERAPY OF DERMATOSES

Samuel M. Bluefarb

Department of Dermatology, Northwestern University Medical School, Chicago, Ill.

Primary and secondary dermatoses occur so frequently that every physician, whether specialist or general practitioner, is likely to observe several such patients daily.[1] Whether he treats the patient or refers him to a dermatologist, it is necessary for the physician to offer competent advice regarding therapy. It is probable that the dermatologist employs a greater percentage of the 5000 pharmaceutical preparations now estimated to be available[2] than do other medical specialists. Because it is not possible for any physician to evaluate in his own practice every new product that the United States Food and Drug Administration considers "safe," he must rely upon the results of clinical investigations performed by competent research groups or private practitioners. Unless clinical investigations such as these are performed, the claims of a manufacturer could be the criteria for employing a new product, and outmoded therapeutic regimens would be perpetuated.

Early in 1958 my colleagues and I were apprised of Triburon, a new topical antimicrobial agent, which was then an experimental drug. The laboratory reports and results of studies on humans[3, 4] indicated that this preparation was tolerated well and caused minimal irritation, that it had a high bacteriostatic and moderate bactericidal activity against a great variety of organisms, and that it was difficult to elicit bacterial resistance. It was found to be active against both Gram-positive and Gram-negative organisms, as well as against some fungus and other infections (that is, *Candida albicans* and *Trichomonas vaginalis*). Robinson and Harmon[5] reported excellent results following Triburon therapy among 50 patients with impetigo contagiosa, in which *Staphylococcus aureus* and *Streptococcus pyogenes* were most frequently demonstrated.

It is well known that prompt therapy is essential for pyogenic infections, since even the localized form may be a potential source of a more diffuse or generalized infection. Any cutaneous infection is a contributing factor to inhibition of the "self-repairing" ability of the tissues.[6] When a pyogenic infection becomes chronic it becomes more resistant to therapy. There are two advantages to topical therapy: (1) bacteria resistant to a systemic drug will probably be sensitive to the topical agent, and (2) if resistance to topical medication occurs, the systemic drugs may be reserved for severe internal infections.[1]

In our studies with Triburon, we were concerned mainly with the clinical results and the incidence of reaction or sensitization. Although the ideal method for these investigations would have included bacteriological studies in all cases, it was neither practicable nor required in the majority and was done only in unusual cases.

* Triclobisonium chloride, product of Hoffmann-La Roche Inc., Nutley, N. J.

Materials and Methods

Triburon therapy was used with 380 patients who were observed at the dermatology clinic of a large county hospital during 9 months. These patients were separated into 2 groups: (1) those given Triburon (plain) ointment and (2) those given Triburon plus hydrocortisone.

In Group 1 there were 161 patients with an approximately equal distribution of men and women and of boys and girls, as well as of children and adults. Their ages ranged from 1 month to 77 years. The cutaneous lesions, in order of frequency, included pyoderma, impetigo contagiosa, eczema, stasis dermatitis, infectious eczematoid dermatitis, seborrheic dermatitis with pyoderma, mycotic infections, and others (TABLE 1). Although the majority of these patients were treated shortly after onset of the infection, the condition had been

TABLE 1
TRIBURON (PLAIN) OINTMENT*
Results of Therapy

Diagnosis	Cured	Improved	No change	Worse	Total
Pyoderma	12	60	17	0	89
Impetigo contagiosa	0	13	1	0	14
Seborrheic dermatitis with pyoderma	1	3	2	0	6
Stasis dermatitis with infection	0	9	0	0	9
Eczema	1	8	1	0	10
Infectious eczematoid dermatitis	2	5	0	1	8
Mycotic infections	0	5	0	0	5
Miscellaneous	3	8	4	5	20
Total	19	111	25	6	161

* Triburon (0.1 per cent) in Carbowax base.

present for from 1 month to several years in a significant number of cases. As a rule, the ointment was applied twice daily, although in some cases it was used 3 or 4 times a day. Treatment was given for 1 week in most instances, and 4 months was the longest period of therapy.

Of the 219 patients in Group 2, 96 were men or boys and 123 women or girls. Their ages ranged from 1 to 78 years, but there were only 27 children in this group. Their cutaneous lesions, in order of frequency, were contact dermatitis, infectious eczematoid dermatitis, lichen simplex chronicus, mycotic infections, psoriasis, eczema, seborrheic dermatitis, and others (TABLE 2). The condition was of short duration in the majority of cases. However, in several patients it had been present for from 1 to 20 years, and some had received several courses of roentgenotherapy. Ammoniated mercury ointment and mild soaks had been used in some, but Triburon was the only therapeutic agent used in the majority of these cases. The application of medication and duration of treatment were similar to those for Group 1. The results were evaluated on the basis of response to therapy and length of time medication was required.

Results

In Group 1, there was complete resolution of the cutaneous lesion in 19 (11.8 per cent) patients, improvement of the condition in 111 (69 per cent), and no change in 25 (15.5 per cent), and the dermatitis became more severe or was irritated by the drug in 6 (3.7 per cent).

One patient in this group was a 3-year-old girl who had atopic dermatitis with secondary infection, which was of long duration and had not improved with any previous therapy. However, the infected lesions resolved after the application of Triburon for 18 days. Another patient, a 42-year-old woman, had infectious eczematoid dermatitis of 6 months' duration that improved greatly following the application of Triburon for 1 week. The youngest patient was a 1-month-old girl who had pyoderma of the scalp. Although the lesions did not improve after 1 week of therapy, there was no apparent reaction to the medication. In this group, 6 adults complained of either irritation or "burning," or both. No evidence of irritation was noted in the children receiving this therapy.

TABLE 2
TRIBURON PLUS HYDROCORTISONE*
Results of Therapy

Diagnosis	Cured	Improved	No change	Worse	Total
Contact dermatitis	30	18	3	4	55
Infectious eczematoid dermatitis	15	11	0	1	27
Pyoderma	4	14	0	0	18
Lichen simplex chronicus	5	13	0	1	19
Mycotic infection	1	9	0	0	10
Tinea pedis	4	5	1	0	10
Eczema	4	4	1	0	9
Psoriasis	1	8	0	0	9
Seborrheic dermatitis	0	7	1	0	8
Nummular eczema	1	4	1	1	7
Stasis eczema	1	4	0	1	6
Erythema multiforme	3	2	0	0	5
Sycosis barbae	0	3	0	0	3
Polymorphous light eruption	1	1	1	0	3
Miscellaneous	6	15	9	0	30
Total	76	118	17	8	219

* Triburon (0.1 plus 0.5 per cent) in Carbowax base.

In Group 2, results on the first 30 patients treated indicated the combination of Triburon and hydrocortisone to be a more effective therapeutic agent than Triburon (plain) ointment. Therefore, this combination was subsequently employed in the majority of cases. In this group 76 (34.7 per cent) of the patients appeared to be cured, 118 (53.9 per cent) showed improvement with this therapy, in 17 (7.8 per cent) the condition was not improved, and eight (3.6 per cent) either had an adverse reaction to the drug or the condition became more severe. Among these patients a 67-year-old man who had moniliasis was well after 1 week of therapy, whereas he had not responded to treatment with

Triburon (plain) ointment. One patient having tinea pedis with secondary infection and one with eczema of the hands, both of approximately 20 years' duration, showed improvement of the lesions after 3 weeks' therapy with the combined ointment, although previously neither patient had improved following roentgenotherapy. In view of the chronicity of the conditions, these cases indicate the dramatic response to Triburon plus hydrocortisone, although most cases in this series were of shorter duration. Among the 8 patients in this series who experienced adverse effects following therapy, 4 who had contact dermatitis noted either pruritus or irritation after 4 days of therapy, irritation after 2 weeks, and irritation after 3 weeks of treatment although, in the last case, the condition had improved during the first 2 weeks. In 1, the lesions of infectious eczematoid dermatitis appeared to be irritated after 1 week of therapy, but improved when medication was discontinued. One patient who had nummular eczema and 1 who had stasis eczema became worse 4 days and 1 month, respectively, following institution of this therapy. Evidence of irritation following therapy occurred only in adult patients.

Comment

The results of treatment revealed that nearly 3 times as many patients in Group 2 as in Group 1 were considered to be cured. This appears to indicate that the addition of hydrocortisone to the base ointment, Triburon, is of definite therapeutic value. The cured cases were approximately 88 per cent of Group 1 and 80 per cent of Group 2.

Although the reactions (3.6 per cent) are higher than desired, analysis of these cases reveals that this incidence is probably not 8 of 219 cases. The fact that a patient complains, or becomes worse 4 days after the initiation of treatment may indicate a response to the disease process, or to the effects of a fixed dressing, to the rubbing in of the ointment, or to a direct primary irritant. Among the 4 patients who evidenced sensitization following at least 2 weeks of therapy, 2 had contact dermatitis, 1 had lichen simplex chronicus, and 1 had stasis eczema. Although this percentage of reaction would be high for an ointment administered to patients generally, it should be remembered that patients having these dermatoses are prone to exacerbations of the condition and are markedly resistant to many therapeutic measures. The fact that none of the 81 children in this series evidenced irritation would indicate that Triburon is not a primary irritant. This is in agreement with the conclusions of other investigators.[4, 5]

Summary

A new antimicrobial ointment, Triburon, was used as topical therapy for 380 patients, ranging in age from 1 month to 78 years, who had various dermatoses. Group 1 consisted of 161 patients who received Triburon (plain) ointment, Group 2, of 219 patients administered an ointment of Triburon plus hydrocortisone.

The majority of patients in the first group had pyoderma or a primary pyogenic infection, while in the second group the cutaneous involvement was usually of an allergic or eczematous nature and, in some cases, was a secondary infection.

As a rule Triburon ointment was applied twice daily and, although the average period of treatment was 1 to 2 weeks, some patients required as much as 4 months of therapy.

The results of this therapy for Groups 1 and 2 revealed that the cutaneous lesions in 11.8 and 34.7 per cent, respectively, were cured; 69.0 and 53.9 per cent were improved; there was no change in 15.5 and 7.8 per cent; and 3.7 and 3.6 per cent evidenced untoward reactions to the preparation.

It is our conclusion that the administration of Triburon plus hydrocortisone is of value for topical application to various cutaneous lesions and is more effective than Triburon (plain) ointment.

References

1. Livingood, C. S. & J. F. Mullins. 1952. Management of bacterial infections of the skin. Postgrad. Med. **12:** 15.
2. Schiffrin, M. J. 1958. Ethics and new drugs. Postgrad. Med. **24:** 305.
3. Schnitzer, R. J., E. Grunberg, W. J. DeLorenzo & R. E. Bagdon. 1959. Triburon, an antimicrobial agent with local activity in living host tissues. Antibiotic Med. & Clin. Therapy. **6** (Suppl. 1) : 61.
4. Edelson, E., E. Grunberg & T. V. Morton. 1959. Clinical appraisal of a new topical quaternary compound, Ro 5-0810/1. Antibiotics Ann. 1958–1959. : 110.
5. Robinson, R. C. V. & L. E. Harmon. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. : 113.
6. Garre, E., R. Ferrario & E. Schillagi. 1959. Topical use of antibiotics in the treatment of chronic skin ulcers. Antibiotics Ann. 1958–1959. : 262.

CLINICAL STUDIES OF THE EFFECTIVENESS OF A NEW TOPICAL ANTIMICROBIAL, TRICLOBISONIUM CHLORIDE

E. Edelson and E. Grunberg
Department of Dermatology, Division of Health and Welfare, Newark, N. J.

A. D. Calabrese and T. V. Morton
Hoffmann-La Roche Inc., Nutley, N. J.

Staphylococcus aureus and *Streptococcus pyogenes* are the organisms most frequently cultured from primary and secondary skin infections. The dissemination of staphylococci has been wide and rapid and is causing particular concern because of the prevalence of numerous strains resistant to many of the modern chemotherapeutic agents.

Recently, a bisquaternary diamine derived from beta-ionone—triclobisonium chloride—was found, that is markedly effective against primary and secondary bacterial infections of the skin.[1, 2]

The chemical formula of this substance is discussed, together with the properties of the compound, elsewhere in this monograph. Of special interest, however, is its activity as a topical antibacterial agent in local infections. Its effectiveness against the various strains of *Staph. aureus* and *Str. pyogenes* has been repeatedly demonstrated both *in vitro* and *in vivo*.[3] Included among these strains were some resistant to penicillin, oleandomycin, tetracycline, erythromycin, chloramphenicol, and multiple or combined antibiotics. Likewise, local activity *in vivo* against strains of *Escherichia coli* has been demonstrated in our series of patients.

It is of further interest that laboratory attempts to produce drug resistance to triclobisonium chloride in experimental *Staph. aureus* strain 209 and *E. coli* strain 503-211 by the serial passage or continuous-exposure methods produced no substantial loss of sensitivity of these organisms to this compound.[3]

Encouraged by these experimental results, two independent groups of investigators carried out initial clinical investigations and found that triclobisonium chloride demonstrated an appreciable effectiveness in the topical treatment of bacterial skin infections.

In our initial study, 113 patients were observed with a maximum evaluation period of 32 days for any 1 patient.[1] Since then we have treated an additional 110 patients for a total of 223 individuals suffering from primary or secondary bacterial infections of the skin. Treatment consisted of boric acid and saline or Burrow's solution compresses, followed by light applications of triclobisonium chloride in a Carbowax base, 3 times a day. No adjunctive therapy, oral or parenteral, was employed during the period of evaluation.

Of the 223 patients, 148 represented primary bacterial infections and the remaining 75 represented secondary types of infections. The types of primary bacterial infections and their clinical responses are summarized in TABLE 1. TABLE 2 gives the same type of summary for 75 cases of secondary and miscellaneous bacterial infections. A summary of the clinical responses of all cases is given in TABLE 3.

TABLE 1

CLINICAL RESPONSE OF PRIMARY BACTERIAL INFECTIONS

	Total	Cured	Moderate to marked improvement	Unimproved
Impetigo contagiosa	108	97	7	4
Sycosis vulgaris	8	6	2	
Folliculitis acute	12	10	2	
Furunculosis acute	3	1	1	1
Furunculosis chronic	4	1	1	2
Folliculitis keloidalis	2	1	1	
Infectious eczematous dermatitis	11	10	1	
Total	148	126 (85.1%)	15 (10.1%)	7 (4.8%)

TABLE 2

CLINICAL RESPONSE OF SECONDARY AND MISCELLANEOUS BACTERIAL INFECTIONS

Infections	Total	Cured	Moderate to marked improvement	Unimproved*
Secondary (superimposed)				
Tinea capitis	30	19	4	7
Tinea circinata	2	2		
Dermatophytosis	5	4	1	
Varicose ulcers	8	7		1
Seborrheic dermatitis	7	6	1	
Erythema multiforme	1	1		
Dermatitis factitia	2	1	1	
Lupus erythematosus	2	2		
Pediculosis pubis	1	1		
Intertrigo	2	1		1
Excoriation (neurotic)	1	1		
Dermatitis venenata	8	6	1	1
Perieche	1	1		
Paronychia	2	2		
Miscellaneous				
Hydradenitis suppurativa	2	2		
Granuloma pyogenicum	1	1		
Total	75	57 (76%)	8 (10.7%)	10 (13.3%)

* The higher failure rate (13.3 per cent) seen with this group is due to the fact that 7 of the failures were secondarily infected patients with tinea capitis of the Audouini type, which, in our clinic, has been severe, the bacterial infections in these patients involving 50 per cent or more of the surface of the scalp.

TABLE 3

SUMMARY OF THE CLINICAL RESPONSE OF PRIMARY, SECONDARY, AND MISCELLANEOUS BACTERIAL INFECTIONS*

Total	Cured	Moderate to marked improvement	Unimproved
223	183 (82.1%)	23 (10.3%)	17 (7.6%)

* In none of the patients were there clinical indications of either sensitization or irritation.

One of us (A.D.C.) expanded this clinical study of the effectiveness of triclobisonium chloride under somewhat different circumstances—namely, under his close supervision in an industrial plant dispensary, where patients could be

TABLE 4

DISTRIBUTION OF INJURIES AND INFECTIONS IN 92 ADDITIONAL PATIENTS STUDIED

Lacerations, abrasions, or avulsions (uncomplicated)	51
Puncture wounds (uncomplicated)	7
Abrasions (secondarily infected)	8
Folliculitis	2
Furunculosis	4
Carbuncle	1
Cellulitis (nonsuppurative)	1
Burns (first and second degree)	7
Impetigo	1
Herpes zoster (secondarily infected)	1
Miscellaneous superficial pyodermata of the arms, legs, and neck	9
Total	92

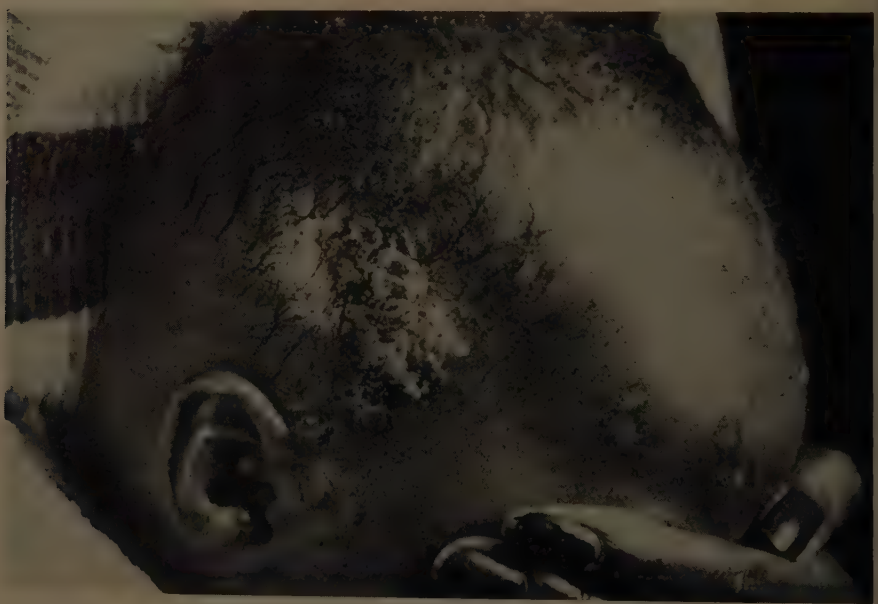


FIGURE 1. Secondarily infected infantile eczema of a 5½-month-old child. Both *Staph. aureus* and *Str. hemolyticus* were originally isolated.

seen daily or, more or less, as often as desired by the observing physician. Thus, 92 additional patients with injuries and infections were studied (TABLE 4).

The majority of these patients were treated for from 3 to 12 days. Applications of triclobisonium chloride were made 2, 3, or 4 times per day, depending on the nature of the condition. The ointment was simply and topically applied

FIGURE 2. Response to therapy, including negative cultures, was complete within 2½ weeks.

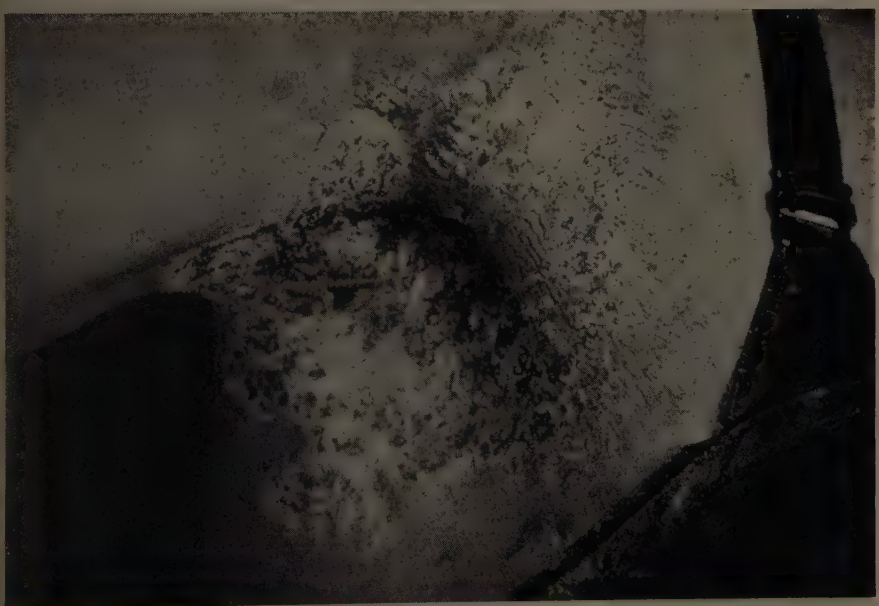


FIGURE 3. Hydradenitis suppurativa with infectious eczematoid dermatitis in a 30-year-old female. Cultures were positive for *Staph. aureus*, *Staph. albus*, and *Str. hemolyticus*.

in some instances, while gauze well impregnated with it was used in treating the burned and some of the abraded patients. Wet dressings applied before the triclobisonium chloride were used as indicated.

Eighty-nine of these 92 patients showed a good response, including the cured and markedly improved. Of the 3 remaining patients, 2 with furunculosis required incision and drainage, and 1 burn patient showed clinical local intolerance to the preparation. Subsequent to the latter's recovery, he was not avail-

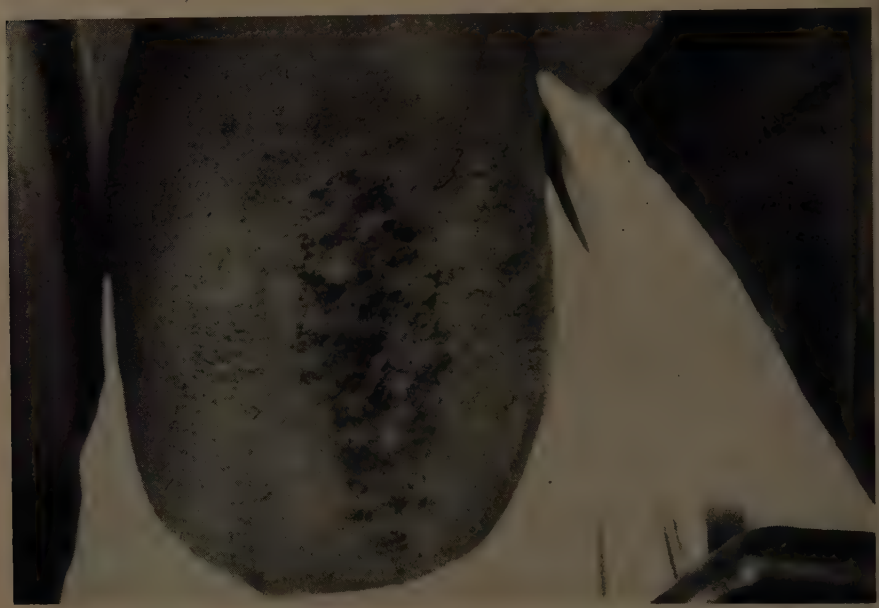


FIGURE 4. Healing at the end of 1½ weeks with negative cultures. The results are extremely suprising, and no claim will be made for the effectiveness of triclobisonium chloride in hydradenitis suppurativa as a routine medication until additional similar results have been reported. However, the improvement in the infectious eczematoid dermatitis is compatible with the demonstrated effectiveness of triclobisonium chloride.

able for determination of whether this intolerance was due to the base or to the triclobisonium per se.

While preliminary sensitization and irritation tests had been performed before beginning the clinical studies, more extensive sensitization and irritation evaluations were made, using the Food and Drug Administration technique (Draize), simultaneously with the early phases of the clinical investigations. These sensitization tests were applied in 10 repeated patch tests, permitting 48 hours of closed contact, with subsequent removal and replacement by a similar patch. The patches contained 0.5 gm. of 0.1 per cent triclobisonium chloride in its water-miscible base. An additional control patch was similarly applied with each change of the medication patch. The control consisted of the water-miscible vehicle alone. Subsequent to the removal of the tenth patch, a 14-day rest period was permitted. At the expiration of this latent period a similar

pair of closed patches (triclobisonium chloride ointment and a control vehicle patch) were applied. These were removed and the results read and recorded 48 hours later; 24 hours thereafter, delayed readings were taken.

Two hundred and nine volunteers completed the full program of 3 weeks of sensitization patches, a 2-week rest period, and the challenge testing. Only 4 subjects (less than 2 per cent) developed allergic responses to triclobisonium chloride as a result of the challenge tests; three indicated allergic reactions to the base alone. None of these reactions, either to the medicament or to the base, was of more than 2++ severity.

TABLE 5

RESULTS WITH 43 PATIENTS TREATED WITH 0.1 PER CENT TRIBURON PLUS 0.5 PER CENT HYDROCORTISONE*

	Cured	Marked improvement	Improved	Unimproved
Impetigo contagiosa	7	2		
Sycosis vulgaris	2			
Folliculitis acute	2	1		
Hydradenitis suppurativa	1			
Infectious eczematoid dermatitis	2	1		
Secondarily infected dermatitides				
Seborrheic dermatitis		1		
Neurodermatitis	2	1		
Atopic dermatitis	2	2	1	
Nummular eczema	2	1		
Dermatitis venenata	5	1	1	
Moniliasis	1			
Intertrigo		2		
Stasis ulcer	1			
Tinea capitis		1		1
Total	27	13	2	1
Percentage	62.8%	30.2%	4.6%	2.3%
	93%			

* Subsequent to the preparation of this table, additional patients recovered, raising our cure rate almost to the combined total of cures and marked improvements shown above. Furthermore, other patients, listed as displaying lesser degrees of success, have improved, changing their response status.

Coincidentally with these clinical and sensitization studies, an additional evaluation was performed on 43 patients with a similar selection of pyodermata and using the same concentration (0.1 per cent) of triclobisonium chloride plus 0.5 per cent of hydrocortisone in the same water-miscible base. The tabulated results of this phase of the studies are shown in TABLE 5.

In conclusion, we feel that the results with the 368 patients with various types of pyodermata as detailed in this study and the additional patients who bring our total to more than 500 cases of bacterial skin infections have demonstrated that triclobisonium chloride is clinically effective as a topical agent in the therapy of primary and secondary bacterial infections of the skin, and that in our studies it has been clinically nonsensitizing. When aided by the anti-inflammatory influence of hydrocortisone, its effectiveness is enhanced espe-

cially in eczematous conditions and accelerates the initial improvements observed in those patients with the more marked associated inflammatory reactions.

Addendum

Subsequent to the completion of the studies detailed in this report, additional patients have been treated regularly at our clinic for related pyodermata, with essentially the same percentages of cure and improvement. None has demonstrated a proved clinical sensitivity to triclobisonium chloride. Other vehicles, including aerosol-type sprays and lotions, have been used.

References

1. Edelson, E., E. Grunberg & T. V. Morton. 1959. Clinical appraisal of a new topical quaternary compound Ro 5-0810. Antibiotics Ann. 1958–1959. : 110.
2. Robinson, R. C. V. & L. E. Harmon. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. :113.
3. Schnitzer, R. J., E. Grunberg, W. F. DeLorenzo & R. E. Bagdon. 1959. Triburon, an antimicrobial agent with local activity in living hosts. Antibiotics & Chemotherapy. **9**(5): 267.

EVALUATION OF A NEW TOPICAL MICROBICIDE IN DERMATOLOGICAL PRACTICE

F. T. Becker and J. L. Tuura
Department of Dermatology, Duluth Clinic, Duluth, Minn.

Despite the large number of antimicrobials available for use in dermatoses and superficial infections, we are continually seeking new agents with a higher therapeutic index. To a large extent antibiotics have replaced many of the older medicaments in dermatological practice. However, the increasing incidence of allergic contact reactions to topical antibiotics makes the use of some undesirable.[1] There is almost universal agreement that antibiotics that have value in systemic infections should not be used topically.[2-4] Increased organism resistance and sensitivity reactions following topical use may preclude subsequent administration of a particular antibiotic when serious systemic infections occur. *Staphylococcus*, for example, almost always present in moderate to severe infected eczema,[5] has shown resistance to a variety of antibiotics with particular frequency.[6] Since pyogenic infections of either primary or secondary types are often open lesions, there is always the possibility of disseminating resistant organisms. There is also evidence that the widespread systemic use of antibiotics may result in cutaneous infections caused by antibiotic-resistant organisms.[2] This may explain why so many skin infections fail to respond to antibiotic therapy. Chemotherapeutic agents, on the other hand, in general act as effectively as topical antibiotics without posing the above problems.

With these considerations in mind, a study was undertaken with a recently reported[7, 8] broad-spectrum topical microbicide, triclobisonium chloride. This new synthetic compound appeared to have particular value since it is a bis-quaternary agent, not an antibiotic, sulfonamide, or nitrofuran. In view of the increasing number of antibiotic-resistant strains, particularly penicillin-fast staphylococci, the usefulness of this agent should be significantly increased. Moreover, from a cosmetic point of view it seemed excellent for topical use.

Triburon* has a marked activity against most of the common skin pathogens *in vitro* and *in vivo*. It is highly active against staphylococci and streptococci regardless of their resistance to antibiotics. Robinson and Harmon[7] found that in pyodermas that responded to Triburon, *Staphylococcus aureus*, *Staph. albus*, and *Streptococcus pyogenes* were the organisms most frequently found. Attempts to develop Triburon-resistant strains by serial-passage methods produced comparatively little change in organism sensitivity. With regard to adverse symptomatology, Edelson *et al.*[8] found that "no evidence of irritation or sensitization was encountered during the clinical trial, and less than 2 per cent allergic response was obtained by the closed-patch technique in 209 individuals . . . ."

It has been pointed out[9] that combinations of corticosteroids and antimicrobials may cause a contact dermatitis that is an allergic reaction to the antimicrobial component. Because of the minimal incidence of sensitization reported with Triburon, we decided to investigate also the combination of

* Triclobisonium chloride, product of Hoffmann-La Roche Inc., Nutley, N. J.

Triburon and hydrocortisone in those patients in whom anti-inflammatory and antipruritic medication seemed desirable.

Case Material

The study comprised 162 office and clinic patients with a wide variety of dermatoses and superficial infections—both primary and secondary (TABLE 1). The following organisms were cultured from infected lesions: *Staph. aureus*, *Staph. albus*, *pseudomonas*, *Proteus*, beta hemolytic streptococci, *Aerobacter aerogenes*, *Escherichia coli*, *Candida albicans*, *Trichophyton mentographytes*, and *T. rubrum*.

TABLE 1
SUMMARY OF RESULTS

Diagnosis	No. of patients	Results					
		Excellent	Good	Fair to good	Fair	Poor	No response
Eczema	51	8	29	3	8	3	
Ulcer	8		6		2		
Dermatitis venenata	3		2			1	
Neurodermatitis	4	2	1			1	
External otitis	3		3				
Dyshidrosis	17		13	1	3		
Pyoderma	13	2	8	1	1		1
Sycosis barbae and vulgaris	5	2	2		1		
Impetigo	5	2	3				
Pemphigus	1		1				
Pruritus vulvae	1					1	
Infected eczematoid dermatitis	4		3		1		
Epidermophytoses	4		1		2		1
Seborrheic dermatitis	1	1					
Psoriasis	3	1	2				
Total	123	18	74	5	18	6	2

Patients were treated with either 0.1 per cent Triburon ointment, plain or together with 0.5 per cent hydrocortisone. Adjunctive therapy consisted of antihistamines, tranquilizers, sedatives, and supportive topical therapy. Several patients received systemic antibiotics. Of the original 162 patients, 123 were observed for a sufficient period at the time of reporting to obtain an adequate clinical impression.

Results

Results were evaluated clinically on the basis of the following criteria: improvement in eczema, control of infection, wound healing, and reduction in pruritis. Response was classified as "excellent," "good," "fair to good," "fair," and "poor." An over-all good response was obtained in 115 of the 123 patients (93.5 per cent). Only one showed no response, and this was a case of inflammatory tinea barbae that improved upon subsequent fungicidal therapy.

One patient with pyoderma scalp showed no change within 1 week, and was given Achromycin systemically.

In general, Triburon and Triburon HC* were highly acceptable to the patient. No irritation, itching, or systemic side reactions were noted, except in one patient who was unable to tolerate the ointment containing hydrocortisone and in one who reported increased pruritus.

In secondarily infected eczemas, the effect on the eczematous process was generally not as striking as was the control of the infection. In some cases, however, both the eczema and infection responded to therapy. Fungal infestations generally showed only a fair response. Triburon did not appear to hinder healing, and in 1 case of carbuncle its application following incision and drainage actually appeared to promote prompt and rapid healing of a large ulcerative defect. Similarly, in a patient allergic to neomycin, healing of stasis ulcers was observed in 2 months of Triburon treatment alone. Of the 5 cases of impetigo, 4 cleared within 4 to 10 days, and 1 patient showed a good response. Triburon produced a better response than any previous medication in 3 cases of otitis externa from which *Pseudomonas* was cultured. One patient with infected eczematoid dermatitis (ear) of 30 years' duration who was resistant to all antibiotics except chloromycetin exhibited rapid improvement following therapy with Triburon.

Comments

Clinical trial with Triburon and Triburon with hydrocortisone in a random sample of patients exhibiting common dermatoses and superficial infections indicates that this compound is not so rapidly effective on superficial pyoderma (impetigo) as some antibiotics. It was, however, more effective in secondarily infected eczematoid eruptions, ulcers, or epidermaphytosis infected with saprophytic coagulase, negative staphylococci, *Pseudomonas*, and *Proteus vulgaris*.

The high degree of efficacy together with an unusually low incidence of sensitivity or allergic reactions (less than 2 per cent in our study) makes Triburon a valuable addition to the dermatological armamentarium. In view of the increasing number of antibiotic-resistant strains and the frequency of hypersensitivity reactions encountered with currently used agents, this antimicrobial merits routine clinical trial in the common dermatological conditions.

Summary

One hundred and sixty-two patients with a diversity of superficial infections and dermatoses were treated with triclobisonium chloride, a new broad-spectrum topical microbicide, both alone and with hydrocortisone.

Favorable results were obtained in 93.5 per cent of the 123 patients followed up.

Except for 2 patients, Triburon and Triburon with hydrocortisone were tolerated unusually well. No adverse systemic effects were encountered.

* Triburon with hydrocortisone.

References

1. Current Concepts in Therapy. 1958. Antibiotics. IV. Topical therapy. New Engl. J. Med. **258:** 947.
2. Nelson, C. T. & M. B. Sulzberger. 1959. Inclusion of antibiotics in cosmetic preparations. Committee on cosmetics, report to the committee. J. Am. Med. Assoc. **169:** 1626.
3. Mescon, H. 1958. Eczematous hand eruption: etiology and treatment. Med. Clin. N. Am. : 1361.
4. Nelson, C. T. 1957. Pustular dermatoses. *In* Current Therapy. : 468. H. F. Conn, Ed., Saunders. Philadelphia, Pa.
5. Sullivan, T. J. & E. M. Farber. 1959. The problem of hand eczema. Postgrad. Med. **25:** 243.
6. Neil, A. J. 1958. Increased resistance to antibiotics among microorganisms isolated in a general hospital, (1956–1957). New York J. Med. **58:** 3102.
7. Robinson, R. C. V. & L. E. Harmon. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. : 113.
8. Edelson, E., E. Grunberg & T. V. Morton. 1959. Clinical appraisal of a new topical quaternary compound, Ro 5-0810/1. Antibiotics Ann. 1958–1959. : 110.
9. Sulzberger, M. B., V. H. Witten & A. W. Kopf. 1958. The topical and systemic use of corticosteroids in the treatment of skin diseases. Postgrad. Med. **24:** 379.

TRIBURON IN DERMATOLOGICAL PRACTICE

Paul L. Williams
Doctors Hospital, Seattle, Wash.

Antibiotic-resistant staphylococci have become so widespread in this country as to constitute a major challenge to medicine in general.[1, 2] The dermatologist especially has been very much concerned with this problem because a large part of his daily practice deals with skin diseases in which staphylococcic infection is the primary etiological factor or constitutes a common cutaneous complication.[3] In every case, however, the pyogenic complication demands attention and elimination before the fundamental skin disease can be treated effectively.

Most certainly, dermatologists are not alone in their concern with the problem; witness the concerted efforts of doctors and health agencies everywhere in their attempts to analyze and combat this problem by both prophylactic and direct methods. However, these efforts have met with but meager success. In spite of the introduction of new and different antibiotics, there continue to emerge mutant strains of staphylococci completely unresponsive to any of the well-known or widely used antibiotics.

As for dermatology, this problem touches close to home, since the skin is one of the major organs attacked by these unique organisms. The increasing frequency with which these frustrating infections are encountered has furnished the impetus for a continued search for more reliable antibacterial agents. Since there is no modern panacea, there has been a tendency among physicians to resort to older topical medications in management of chronic cases resistant to, or intolerant of, antibiotics. These include the mercurials, iodine, gentian violet, and others, in spite of the well-known inherent disadvantages of repeated application of these to skin or mucous membranes, or both.

In this day of synthetic chemistry, it would appear both rational and feasible that eventually the ideal topical agent with specific wide-range antibacterial action should come to light. It would be a compound that would exhibit in practice two highly desirable characteristics; effectiveness against all strains of staphylococci, regardless of their resistance to antibiotics, and freedom from both irritation and sensitization potentialities when applied repeatedly to inflamed skin in a therapeutically effective concentration. The microbicide Triburon* has been synthesized through research directed toward chemical compounds unrelated to the antibiotic field.

Confronted with patients presenting recalcitrant or recurring pyogenic skin infections, and having in mind the aforementioned requirements in a drug, I welcomed the opportunity to have Triburon available for clinical evaluation in my dermatological practice. This new antimicrobial agent in both *in vivo* and *in vitro* tests exerted an anticoccal effect, particularly against staphylococci, regardless of sensitivity or resistance to antibiotics.[4] Clinical studies involving a variety of dermatoses and infective organisms showed this medication to be effective in more than 80 per cent of the cases treated.[5, 6]

* Hoffmann-La Roche.

Materials and Methods

A total of 84 patients in 2 groups was treated with Triburon or Triburon plus hydrocortisone. Among the variety of dermatoses treated were a few primary infections, but the majority were conditions resulting from secondary infections. The ages of the patients treated, similar for both groups, ranged from 7 months to 75 years. There were 3 children in Group 1, and 4 in Group 2. Treatment periods ranged from 3 days to 3 months.

TABLE 1

SUMMARY OF EXPERIENCES WITH TRIBURON AND TRIBURON PLUS HYDROCORTISONE

Diagnosis	No. patients	Response				No follow up
		Healed	Excellent	Good	No improvement	
Triburon						
Psoriasis	7	1*	2	2	1	1
Folliculitis	5	4	1	—	—	—
Furunculosis	6	1	4	1	—	—
Intertrigo crural	3	1	2	—	—	—
Atopic dermatitis	2	—	2	—	—	—
Contact dermatitis	2	1	—	—	—	1
Eczematoid dermatitis	4	2	2	—	—	—
Miscellaneous	12	3	7	1	—	1
Total	41	13	20	4	1	3
Triburon plus hydrocortisone						
Atopic dermatitis	11	1	10	—	—	—
Neurodermatitis	10	3	7	—	—	—
Eczema	8	5	2	—	—	1
Contact dermatitis	6	1	3	1	—	1
Lichen simplex chronicus	3	—	2	1	—	—
Pruritus ani	3	1	1	—	1	—
Miscellaneous	2	2	—	—	—	—
Total	43	13	25	2	1	2

* Dramatic improvement attributed to steroids given concomitantly, although Triburon was an excellent adjunctive medication.

Group 1 consisted of 41 patients who were treated with Triburon ointment and soaks. The conditions treated were infected psoriasis, folliculitis, furunculosis, intertrigo, infected atopic dermatitis, infectious eczematoid dermatitis, and 12 others listed as miscellaneous because there was only 1 patient in each category (TABLE 1). The majority of patients had received therapy that consisted of topical and systemic antibiotics, antihistamines, tranquilizers, topical steroid medication, epsom salts soaks, vitamins, and X rays. When started on Triburon therapy, soaks or wet dressings were used when warranted by the presence of inflammation. The patients were advised to apply wet Triburon compresses for 30 or 40 min. once or twice daily. This was followed in most cases by application of the ointment; when the ointment was used alone,

applications t.i.d. were usually prescribed. Burrow's solution and other soaks and cleansing agents were used adjunctively in 9 patients; 1 patient (intertrigo crural with folliculitis) received 600,000 U. of penicillin, I.M.; 1 patient received an oral sulfa; 4 received systemic steroids or antihistamines; and 1 was treated with Grenz irradiation.

In Group 2 there were 43 patients who received Triburon plus hydrocortisone. Eleven patients had atopic dermatitis and 10, neurodermatitis. The diagnoses of the remaining cases included eczema, contact dermatitis, lichen simplex chronicus, pruritus ani, intertrigo axillaris with hyperhidrosis, and secondarily infected acne rosacea. Prior therapy in this group included systemic antibiotics, antibiotic, steroid, antihistamine, and Panthenol creams; and Vaseline, Caladryl lotion, X-ray treatment, and soaks. Triburon was applied t.i.d. in all but 2 patients, who used it b.i.d. Adjunctive therapy employed in 10 patients included antipruritic medication, tranquilizers, corticosteroids, and bland cleansers.

Organisms were cultured and blood studies performed when warranted. Results were based on objective and subjective observations, taking into account the type and chronicity of the disease.

Results and Conclusions

Results with both formulations of Triburon were remarkably good. In Group 1, 13 patients showed complete healing, 20 had excellent results, and 4 showed a good response to therapy. In only 1 patient was there no improvement of a chronic psoriasis of the legs of 8 years' duration. It was not possible to obtain any follow-up data on the remaining 3 patients in this group.

In Group 2, 13 patients were cured. The response was excellent in 25 and good in 2, and there was no improvement in 1; 2 were lost to follow-up. The patient who did not improve had had pruritus ani for 4 years, but there was no objective evidence of skin disease, and the patient's complaints occurred principally when he was not distracted by other activities.

Those whose improvement was described as excellent had complete clearing of the secondary infections, with almost complete disappearance of the underlying allergic exacerbations. Twelve patients in whom *in vitro* studies demonstrated penicillin resistance responded rapidly to the new drug. The majority of cultures obtained showed the presence of *Staphylococcus aureus*, but *Streptococcus hemolyticus*, coagulase positive, was also isolated.

Triburon was observed to be virtually nonsensitizing and nonirritating to skin and mucous membranes. There were only three cases of transient burning sensations on initial application, without concomitant objective evidence of irritation. The unpleasant sensation subsided with subsequent applications.

In several cases where there was resistance to topical steroid medications containing neomycin, it was thought that increasing the concentration of the steroid would improve the response. Experience with Triburon hydrocortisone (HC) indicated, however, that the failure to heal was due to resistance of the bacterial contaminant to neomycin, because Triburon, with the same strength (0.5 per cent) of hydrocortisone, accomplished healing when the previous medication had failed.

Summary

Eighty-four patients with a variety of acute and chronic infective dermatoses were treated with a new topical antimicrobial, Triburon, with or without the addition of hydrocortisone. The patients ranged in age from 7 months to 75 years and treatment varied from 3 days to 3 months.

Usually the ointment was applied t.i.d. When Triburon solution was used compresses were applied 30 or 40 min. once or twice daily.

The dermatoses healed completely in 26 patients; 45 had an excellent response to therapy; 6 showed a good response; 2 remained unimproved; and 5 patients could not be evaluated since they did not return for treatment. Of the 79 patients whose response to Triburon was noted, 77 showed improvement ranging from good to complete.

The only side effects noted were 3 cases of a transient burning sensation that subsided even on continuation of the drug.

Triburon was found to be a valuable nonantibiotic synthetic compound for the direct elimination of bacterial skin infections.

Case Studies

E.H., a 24-year-old white female, had cyclic vesiculopustular eruptions of the palms for 2 years, which recurred during the premenstrual period. Her current condition was diagnosed as dyshidrotic eczema with secondary infection. Laboratory cultures showed the presence of *H. staph. aureus* sensitive to Triburon. Previous therapy with an antibacterial cream and potassium permanganate soaks had not been effective. After only 4 days of Triburon applications, rather dramatic healing occurred, with pustulation and acute inflammation controlled. Eleven days from the start of therapy all evidence of infection was controlled, and the dry eczematoid patches were in the healing phase.

L.W., a 31-year-old housewife, had an acute furuncular abscess of 1 weeks' duration. The clinical picture was that of an incipient furuncle on the right leg with an ulcerative pyogenic surface surrounded by a large area of intense erythema. Epsom salts baths had not helped. Cultures showed the presence of many *Staph. aureus*, coagulase positive. The infection may have been contracted from her husband who, for the previous 5 months, had had recurring furuncles following hospital discharge after nephrectomy. The patient was advised to use Triburon wet hot packs daily, followed by Triburon ointment dressings. When seen on the third day of therapy the abscess was localizing with drainage and sloughing, leaving a clean base. The surrounding erythema had subsided, and the patient no longer complained of marked pain. Four days later (1 week after the initiation of Triburon therapy) the infected area was entirely healed.

C.K., a 56-year-old male, reported with an extensive acute folliculitis barbae of 7 days' duration. He had numerous folliculo-vesicular-pustular and inflammatory lesions of the entire beard area with patchy, moist, squamous lesions extending to the ears. This condition caused intermittent moderately intense itching. An antipruritic agent was employed to control the itching, and warm Triburon compresses (1:1000), were applied for 30 min. twice daily.

His condition was completely cured in 72 hours with no evidence of recurrence in any previously involved area. This was one of the most dramatic cures I have observed, in view of the extensive and well-established infection present on the initial visit. The patient plans to use the solution as an after-shave lotion for prophylactic effect.

A.B., a 70-year-old male, had eczema for 6 years with periodic exacerbations. His previous treatment had consisted of antimicrobial drugs. When seen, the patient had a secondary infection and excoriated eczema. Cool Burrow's wet dressings were applied b.i.d. adjunctively with Triburon. After 1 week his condition was much improved, with no evidence of active pustulation. The patient remarked that 1 week of Triburon therapy had accomplished more than 1 month of other antimicrobial therapy in the past.

L.R., a 34-year-old male with a chronic neurodermatitis manifest for 2 years exhibited typical lesions of eczema nuchae of the seborrheic type. From the patient's manner and appearance it appeared that neurogenic factors definitely contributed to the symptomatology. Triburon plus hydrocortisone was applied t.i.d. In spite of the chronicity, all lesions healed in only 1 week. Objectively, the previous scaly area appeared normal and free of inflammation. While the patient received a tranquilizer concomitant with the Triburon HC, even this could not account for the objective improvement, which was entirely unanticipated.

R.L., a 19-month-old boy referred to us by his pediatrician, evidenced infected atopic dermatitis that was particularly severe on the face and scalp. His condition had persisted for 2½ months, during which time he had received local and systemic antibiotics without benefit. He showed intolerance of chloromycetin, and a neomycin-hydrocortisone ointment had previously caused irritation. When first seen, this baby had numerous crusted, serosanguineous, and infected eczematous lesions on the face and scalp, with marked boggy lymphadenopathy over the inferior occipital scalp. He had been hospitalized, but was discharged, unimproved, on systemic tetracycline; he was febrile. Triburon wet dressings applied for 30 min. b.i.d. were followed by Triburon cream. Within 1 week he showed improvement with diminished crusting and with clearing of the pustules and exudations. By the ninth day he was very much improved and afebrile. One month after initiation of Triburon dressings his face and scalp were healed, with a minimum of macular erythema only in spotty areas on the face. The scalp was remarkably healed and the pronounced boggy lymphadenopathy, which called for skull X ray in the hospital, had subsided completely.

W.H., a 43-year-old male, was the only patient in this series with burn. He had a second-degree thermal burn in a localized area on the arm. Despite the fact that it had occurred only the day before he reported for treatment, it was erythematous, with a diffuse edematous bleb. After treatment in the office, home treatment with Triburon solution compresses 40 min. daily were prescribed. Eight days later the burn area was completely healed.

References

1. Yow, M. D., M. M. Desmond & L. N. Nickey. 1959. The management of staphylococcal disease in infants and children. J. Pediat. 54: 409.

2. Weil, A. J. 1958. Increased resistance to antibiotics among microorganisms isolated in a general hospital (1956–1957). N. Y. State J. Med. **58:** 3102.
3. Andrews, G. C., A. N. Domonkos & C. F. Post. 1951. Treatment of acne vulgaris. J. Am. Med. Assoc. **146:** 1107.
4. Schnitzer, R. J., E. Grunberg, W. F. DeLorenzo & R. E. Bagdon. 1959. Triburon, an antimicrobial agent with local activity in living host tissues. Antibiotics & Chemotherapy. 9: 267.
5. Edelson, E., E. Grunberg & T. V. Morton. 1959. Clinical appraisal of a new topical quaternary compound, Ro 5-0810/1. Antibiotics Ann. 1958–1959. : 110.
6. Robinson, R. C. V. & L. E. Harmon. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. : 113.

THE USE OF TRICLOBISONIUM CHLORIDE (TRIBURON*) IN PEDIATRIC PRACTICE

S. Bielinski, J. M. Fox, A. B. Falk
Children's Memorial Hospital and University of Illinois Research and Educational Hospitals, Chicago, Ill.

Although there are many effective medications for topical treatment of skin eruptions, the addition of a new therapeutic agent is welcome. The application of external medications directly and repeatedly to skin lesions is one of the most important measures in treating dermatoses. The efficacy of such ointments or lotions can be evaluated readily by objective critical and comparative observations.[1]

One of the prerequisites of an acceptable topical medicament is that it cause no primary irritation or sensitization. From clinical reports[2, 3] we judged Triburon worthy of investigation in a pediatric dermatological practice. One hundred patients were studied by use of covered patch tests, and Triburon was found to be not a primary irritant. In paired-comparison studies on 38 patients it was shown to be effective, clearing widespread impetigo within 5 days.[3] In studies in which Triburon was used for a wide variety of skin eruptions, results were excellent.[2, 3]

Another aspect to be considered in pediatric practice is the possible ingestion of any topically applied agent. While no human tolerance studies are reported (Triburon is not a systemic drug), in rats and mice oral lethal doses were as high as 375 to 400 mg./kg.; in dogs, lethal doses could not be determined, since a dose of 20 mg./kg. produced emesis.[4] It can be assumed from these studies that the probability of internal toxicity in children would be slight. The amount of ointment sucked from the affected skin would be inconsequential and, if a large quantity were ingested, emesis would probably result.

In the study reported here we used Triburon both with hydrocortisone and plain, in a Carbowax base. The rationale for hydrocortisone is that it is a potent anti-inflammatory and antipruritic agent that produces fast, if temporary, improvement.[5] It has no antibacterial activity.

Methods and Materials

The group under study comprised 52 patients with dermatological disorders, 39 of whom were children. Twenty-eight suffered with eczematous conditions, some of which were complicated by secondary infection, while the remaining 24 could be characterized roughly as exhibiting primary or secondary pyodermas. The former were treated with Triburon and 0.5 per cent hydrocortisone, while the latter received the Triburon (plain) medication.

Group 1 consisted of 13 males and 15 females, whose age ranged from 3½ months to 77 years. Group 2 consisted of 11 males and 13 females, with an age range of 4 months to 40 years. In the pyodermal group all but 2 patients

* Triburon, Hoffmann-La Roche.

were children under 13 and, in Group 1, the ratio of children to adults was nearly 2:1.

The diagnostic categories in Group 1, summarized in TABLE 1, included various types of eczema, dermatitis venenata, neurodermatitis, diaper rash, and tinea pedis. In Group 2 the conditions included ecthyma, eczema and pyoderma, folliculitis, furuncles, and other pyodermas (TABLE 2).

TABLE 1
TRIBURON WITH HYDROCORTISONE

Diagnosis	No. of patients	Results			
		Cured	Improved	Not improved	Reactions
Eczema	7	1	5	1	
Atopic eczema	3		2	1	1 swelling and burning
Infectious eczema	3		3		
Nummular eczema	1		1		
Seborrheic eczema	2	2			
Eczema with pyoderma	1		1		
Dermatitis herpetiformis with secondary pyoderma	1		1		
Dermatitis repens	2		1	1	
Dermatitis venenata	2		2		
Atopic dermatitis with pyoderma	1			1	rash more severe
Neurodermatitis, localized	2		1	1	1 swelling and burning
Epidermolysis bullosa with *Staph. septicemia*	1		1		
Diaper rash	1		1		
Tinea pedis	1		1		
Total	28	3	20	5	3

TABLE 2
TRIBURON OINTMENT (PLAIN)

Diagnosis	No. of patients	Results			
		Cured	Improved	Not improved	Reactions
Ecthyma	1		1		
Eczema (infected with pyoderma lichenified)	4	1	2	1	
Epidermolysis bullosa with pyoderma	1	1			
Folliculitis	1	1			
Furuncles	2		2		
Impetigo	4	2	2		
Inflammatory tinea capitis	1	1			
Kerion	1	1			
Pyoderma	7	5		2	
Pustular bacterid	1	1			
Ulcerating hemangioma	1	1			
Total	24	14	7	3	0

Previous treatment of the patients in Group 1 consisted of medication with Vioform, ammoniated mercury, steroid cream, Whitfield's ointment, and coal tar.

Triburon with hydrocortisone (0.5 per cent) was administered either 3 or 4 times daily and, in 2 patients, twice daily. Duration of treatment varied from 2 days in 2 patients with localized neurodermatitis to 8 weeks in some cases of eczema. Evaluation of results was based on clinical observations and subjective improvement. Signs of irritation or other untoward reaction were noted.

In Group 2, patients' prior treatment consisted of antibiotics (tetracyclines, bicillin, bacitracin), Vioform cream, Aralen, potassium permanganate soaks, 5 per cent iodine ointment, and Whitfield's ointment. Application of the regular Triburon ointment was 4 times daily in most instances. Treatment was continued for from 1 to 8 weeks, depending on the response both as to remission of symptoms and possible development of side effects.

Results

In Group 1, 23 (82.1 per cent) of the patients showed improvement and 5 (17.9 per cent) did not improve. The improvement ranged from 30 per cent to complete clearing of the eczematous condition. The majority of these patients had been treated previously with other medications without success.

One patient who had dermatitis repens of the hands for 1 year and was not responding to various topical medications showed a 50 per cent improvement after 4 weeks of Triburon therapy, with continuing improvement thereafter. A 62-year-old female patient with nummular eczema of the foot, also for 1 year, obtained a 90 per cent clearing of the lesions after 6 weeks. A 12-year-old boy who had infectious eczema of the hands and arms of 5 years' duration improved 75 per cent after 3 weeks of treatment.

Three of the 5 patients in this group who were unimproved had adverse reactions to Triburon. Swelling and burning of the affected sites were noted in 2 patients, although patch tests for Triburon and Carbowax were negative. In the third patient, a 14-year-old girl with atopic dermatitis complicated by pyoderma, pustular lesions became more severe.

In Group 2, 20 (83.3 per cent) of the patients improved, 2 discontinued the drug because their condition became worse, and in 1 there was no change in the pyoderma after 2 weeks of therapy. Of those showing improvement, 14 had complete remission of their dermatitides at the end of 6 weeks, with some responding within 1 week.

Discussion

While the percentage of patients who improved on therapy was similar in both groups, the percentage with total clearing of skin lesions was significantly greater in Group 2, in which infection was the predominating feature of the eruption. It is not felt that the presence of hydrocortisone had an adverse effect in Group 1, but rather that eczematous conditions that are often of an allergic nature will not be cured, but only alleviated by topical ointments. In this respect the results were very satisfactory in Group 1.

It is often difficult to determine the cause of skin eruptions. Nevertheless, as physicians we must institute therapy. When eczematous lesions become secondarily infected, it is necessary to use antibacterial agents directly on the affected areas. For such local applications, it is more desirable to use an agent different from that used for systemic medication,[6] since the bacteria may already be resistant to the drug. Organisms repeatedly subjected to Triburon have been shown to maintain their sensitivity to this compound, whereas the same organisms have become resistant to penicillin.[7]

Summary

Triburon ointment with hydrocortisone was applied 2 to 4 times daily to the affected areas of 28 patients with eczematous conditions, some secondarily infected. There were 18 children and 10 adults in this group. Duration of treatment was from 2 days to 8 weeks. Three of the patients had 100 per cent clearing of symptoms, 20 improved, and 5 did not improve. Two patients experienced swelling and burning at the site of application, and 1 developed a more severe pustular eczema after its use.

Triburon (plain) ointment was applied for from 1 to 8 weeks to skin lesions of 24 patients with primary or secondary pyodermas. In 14 patients the pyodermas cleared completely; in 7 the conditions improved; and in 3 there was no improvement. There were no untoward reactions in this group.

An over-all favorable response was achieved in 82.7 per cent of 52 patients, indicating that Triburon alone or with hydrocortisone is an effective agent in treating many types of dermatoses.

References

1. Sulzberger, M. B. 1958. The choice of dermatologic drugs. *In* Drugs of Choice 1958–1959. : 788. W. Modell, Ed. Mosby. St. Louis, Mo.
2. Edelson, E., E. Grunberg & T. V. Morton. 1959. Clinical appraisal of a new topical quaternary compound, Ro 5-0810/1. Antibiotics Ann. 1958–1959 : 110.
3. Robinson, R. C. V. & L. Harmon. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. : 113.
4. Schnitzer, R. J., E. Grunberg, W. F. DeLorenzo & R. E. Bagdon. 1959. Triburon, an antimicrobial agent with local activity in living host tissues. Antibiotics & Chemotherapy. 9: 627.
5. Welsh, A. L. & M. Ede. 1954. Hydrocortisone ointments: their rational use in dermatology. Ohio State Med. J. **50:** 837.
6. Tudor, R. B. 1958. Eczema, allergic rhinitis, and asthma in infancy and childhood. J.-Lancet. **78:** 373.
7. Schnitzer, R. J. & E. Grunberg. 1957. Drug Resistance of Microorganisms. : 87. Academic Press. New York, N. Y.

Discussion

R. C. V. Robinson (*University of Maryland Medical School, Baltimore, Md.*): The number of antibacterial substances intended for local application has grown to such magnitude that introduction of a new compound can be justified only by proving its superiority to available preparations or by otherwise demonstrating the necessity for its commercial production. The ideal product should be nonirritating and nontoxic, should have a low cutaneous sensi-

tizing potential, must be effective against the usual organisms causing pyodermas, and should be esthetically acceptable to the patient.

Ammoniated mercury ointment, although still widely used in clinical practice, has fallen into disrepute because of its sensitizing and irritating properties. Of the antibiotics intended primarily for local administration, neomycin is most popular, but reports of neomycin sensitivity increase steadily. Hexachlorophene is available in soaps, hand lotion, deodorants, and a host of other toiletries and antiseptics, but also causes contact sensitization reactions, while not possessing the therapeutic effectiveness of the antibiotics. The quaternary ammonium compounds form another group of antibacterials, and an example of this group is triclobisonium chloride (Triburon*), a bisquaternary ammonium compound.

The problem of discussing five papers that contain overlapping material and yet are dissimilar in some respects is necessarily complex. This discussion is therefore divided into three parts: a brief critique of each paper, an over-all summary of the combined findings, and presentation of my experiences with Triburon.

Individual Papers

In Bluefarb's first series of 161 patients, he includes 89 patients with an unspecified type of pyoderma, 12 of whom were cured and 60 improved, while none of 14 patients with impetigo was cured, although almost all were improved. On the other hand, of 10 patients with eczema, 1 was cured and 8 improved, while all 5 patients with mycotic infections were cured.

The findings with the Triburon hydrocortisone ointment are equally bizarre. All of 9 patients with psoriasis were cured or improved, and 8 of 9 patients with eczema were cured or improved. These are better results than would be expected with 0.5 per cent hydrocortisone alone. One would not usually expect such dramatic results in the local therapy of such a systemic disease as erythema multiforme.

If, in each of the series, the patients are divided into two categories—that is, those with pyodermas and those with other conditions—the findings may be summarized as follows:

Bluefarb's results (TABLE 1) indicate that there is no significant difference in the therapeutic efficacy of Triburon on pyodermas and other conditions that he treated.

In the paper prepared by Edelson, Grunberg, Calabrese, and Morton, the authors mention cures in 19 of 30 cases of secondarily infected tinea capitis, in 6 of 7 cases of seborrheic dermatitis, in 2 cases of lupus erythematosus, and in 1 patient with pediculosis pubis. I presumed, and Edelson stated, that the term "cured" applies only to the secondary infection, and does not imply improvement in the primary conditions.

Their results (TABLE 2) in furunculosis surprise me, since these patients, in my experience, do not respond to local therapy alone. The authors discount those patients who were not observed in follow-up visits but, in those observed, no adverse reactions were noted in more than 500 patients. On the

* Hoffmann-La Roche.

basis of the statistics shown, I cannot accept the validity of their statement that the addition of hydrocortisone to Triburon ointment enhances its effectiveness.

In Becker's presentation, those cases treated with Triburon alone were not differentiated from those treated with the hydrocortisone combination. If the

TABLE 1
SUMMARY OF DATA FROM PAPER BY BLUEFARB

Drug	Condition	No. of patients	Results*			
			Cured	Improved	No change	Worse
Triburon ointment, 0.1%	Pyodermas	126	15 (11)	90 (72)	20 (16)	1 (1)
	Other conditions	35	4 (11)	21 (61)	5 (14)	5 (14)
Triburon, 0.1% Hydrocortisone, 0.5%	Pyodermas	48	19 (40)	28 (58)	0	1 (2)
	Other conditions	171	57 (33)	90 (53)	17 (10)	7 (4)

* Figures in parentheses give percentages of total.

TABLE 2
SUMMARY OF DATA FROM PAPER BY EDELSON AND CO-WORKERS

Drug	Condition	Total patients	Patients benefited*	Reactions
Triburon ointment, 0.1%	Pyodermas	223	206 (92.4)	none
Triburon, 0.1% Hydrocortisone, 0.5%	Pyodermas and secondarily infected dermatoses	43	40 (93)	none

* Figures in parentheses give percentages of total.

TABLE 3
SUMMARY OF DATA FROM PAPER BY BECKER

Drug	Condition	No. of patients	Results*			
			Good to excellent	Fair to good	Poor	No follow-up
Triburon, 0.1%, alone or in combination with hydrocortisone, 0.5%	Pyodermas	55	35 (64)	4 (7)	4 (7)	12 (22)
	Other conditions	107	57 (53)	19 (18)	5 (5)	26 (24)

* Figures in parentheses are percentages of total.

results of this study are examined in summary, (TABLE 3) it is seen that, while there is a slightly greater percentage of good-to-excellent results in the treatment of pyodermas, the over-all percentages of "fair, fair to good, good, and excellent" results are identical. This may be accepted as valid since the percentage of inadequately observed cases is the same in the two series.

In view of the beneficial effect of topical application of an antibacterial substance on such diversified dermatoses as dermatitis venenata, dyshidrosis, neurodermatitis, and psoriasis, one wonders about the therapeutic efficacy of the ointment base itself. A control series or paired-comparison studies might have proved helpful in clarifying this.

Williams treated eighty patients with primary pyodermas or secondarily infected dermatoses, with the same beneficial results described by previous speakers. It is noteworthy that his results with Triburon alone were essen-

TABLE 4
SUMMARY OF DATA FROM PAPER BY WILLIAMS

Disease	Beneficial results in observed patients	
	Triburon (plain) per cent	Triburon HC per cent
Psoriasis	86	
Primary pyodermas	100	
Atopic dermatitis	100	100
Contact dermatitis	100	100
Eczema	100	100
Miscellaneous	100	100

TABLE 5
SUMMARY OF DATA FROM PAPER BY BIELINSKI AND CO-WORKERS

Drug	Condition	Results*		
		No. of patients	Improved	Not improved or reacted adversely
Triburon ointment, 0.1%	Pyodermas	24	21 (87)	3 (13)
	Other conditions	—	—	—
Triburon, 0.1% Hydrocortisone, 0.5%	Pyodermas	8	6 (75)	2 (25)
	Other conditions	20	17 (85)	3 (15)

* Figures in parentheses are percentages of total.

tially the same as when similar conditions were treated with the hydrocortisone combination.

Critical evaluation of Williams' results (TABLE 4) would be aided by specific data regarding adjunctive and previous therapy in individual patients. I have had no experience with the Triburon solution that was used in compresses, but I doubt its specific value in unruptured furuncles, unless percutaneous absorption can be proved.

Fox and Falk have discussed chiefly the use of Triburon in dermatoses encountered in pediatric practice (TABLE 5). In their opening paragraph they state: "The application of external medications directly and repeatedly . . . is one of the most important measures in treating dermatoses."

Although the specialty of dermatology has made great strides in specific treatment directed at etiological agents, we are still to a great extent empirical therapists. However, indiscriminate local applications may serve only to irritate or mask a pre-existing eruption. The great numbers of lotions, ointments, and other formulas which we use were born of the vast experience of our predecessors in the field who evolved local therapy that would be of benefit, but would not irritate.

The authors limited the use of plain Triburon ointment to the treatment of pyodermas, and observed improvement in 87 per cent of their patients. The addition of 0.5 per cent hydrocortisone proved therapeutically effective in 85 per cent of inflammatory dermatoses, with or without secondary infection.

Summary Discussion

As with all new drugs, there will be an early tendency to use Triburon ointment as local therapy for many conditions for which it was never intended. It must be remembered that Triburon is an antibacterial substance, and that

TABLE 6
SUMMARY OF RESULTS OF TREATMENT WITH TRIBURON AND TRIBURON HC OINTMENT

Condition	Preparation	No. of patients	Beneficial results*
Pyodermas	Triburon, 0.1%	154	127 (82)
Secondarily infected allergic or eczematous dermatoses	Triburon, 0.1% Hydrocortisone, 0.5%	100	94 (94)

* Figures in parentheses are percentages of total.

there has been no manufacturer's claim of anti-inflammatory or anti-allergic properties. Furthermore, many of the conditions that manifest themselves on the skin merely reflect some underlying systemic disease. Therefore, it is illogical to assume that covering the surface of the body will smother the hidden pathological process and produce a cure. On the other hand, a great many patients with inflammatory or allergic dermatoses will respond, at least temporarily, to locally applied or systemically administered placebo substances.

Hydrocoristone, locally applied in concentrations of 0.5 per cent or greater, has proved effective in relieving the subjective and objective symptoms of inflammatory and allergic dermatoses. It has been further shown that, when it is combined in lotion or ointment vehicles with antibacterial substances, the therapeutic efficacy of each medication is retained and, therefore, antibacterial–steroid combinations are useful in the treatment of secondarily infected eczematous eruptions.

With the above facts in mind, the data contained in three of the papers were analyzed for cases of pyodermas treated with 0.1 per cent Triburon ointment, and for secondarily infected allergic or inflammatory dermatoses treated with the combination of 0.1 per cent Triburon and 0.5 per cent hydrocortisone. The results are outlined in TABLE 6. As indicated by the figures, Triburon alone in the treatment of pyodermas is more than 80 per cent effective. More

impressive results are obtained with the hydrocortisone combination, which afforded benefit in 94 per cent of the patients treated.

Personal Experience with Triburon

In spite of the increasing incidence of antibiotic-resistant systemic infections, most of the currently available antibiotic or antibacterial ointments are effective in the treatment of impetigo contagiosa and ecthyma. This may be explained on the basis of an overwhelming concentration of drug in contact with the infecting organisms. Harmon and I, therefore, treated thirty-eight pa-

TABLE 7

SUMMARY OF 162 PATIENTS WITH PRIMARY PYODERMAS TREATED BY LOCAL APPLICATION OF TRIBURON OINTMENT, 0.1 PER CENT

Condition	No. of patients	Duration of treatment (days)	Patients benefited*	Adverse reactions	No follow-up
Impetigo contagiosa	83	3–10	69 (97)	2	12
Ecthyma	61	5–14	49 (100)	0	12
Pustular folliculitis	18	7–21	14 (87)	1	2

* Figures in parentheses are percentages of total. Only patients in whom follow-up observations were made are included.

TABLE 8

TREATMENT OF SECONDARILY INFECTED ALLERGIC AND INFLAMMATORY DERMATOSES AND PUSTULAR ACNE WITH LOCAL APPLICATIONS OF A COMBINATION OF TRIBURON, 0.1 PER CENT, AND HYDROCORTISONE, 0.5 PER CENT, IN LOTION OR OINTMENT BASE

Condition	No. of patients	Duration of treatment	Results			No follow-up
			Improved	No change	Worse	
Pyodermas	175	1–4 weeks	152	5	3	15
Pustular acne*	67	3 weeks to 4 months	51	10	1	5

* Concurrent systemic administration of Madribon.

tients who had widespread impetigo by the paired-comparison method and, in a previously published report, stated that there was no appreciable difference between Triburon ointment and two commercially available antibiotic ointments.

One hundred sixty-two patients with pyoderma have been treated with Triburon 0.1 per cent in Carbowax or vanishing-cream base. The results are outlined in TABLE 7. Almost all these patients were outpatients of the University Hospital in Baltimore, Md., which explains not only the large number of primary pyodermas (not seen in private practice), but the percentage of patients who were lost to follow-up.

Although the duration of treatment of impetigo is listed (TABLE 7) as 3 to 10 days, patients almost invariably stated that improvement began after 24 hours and, in those observed after 4 or 5 days, lesions were completely involuted.

Observations later than this were made on patients who returned only after 7 to 10 days. Even ammoniated mercury ointment will be effective after 1 week. Ecthyma, being deep-seated impetigo, needs longer treatment. Folliculitis, while improved by the treatment, frequently necessitates the use of systemic antibiotic therapy. I believe that systemic antibiotics, selected by tube dilution or disk-sensitivity tests, are indicated in the treatment of furunculosis.

As stated above, the therapeutic effectiveness of Triburon ointment in the treatment of pyodermas is comparable to that obtained with local antibiotic preparations now available. Wherein, therefore, lies the advantage of this preparation? The answer, in my opinion, is to be found in the use of a Triburon-hydrocortisone combination in the treatment of secondarily infected allergic or inflammatory dermatoses and, with concurrent systemic administrations of Madribon,* in the treatment of pustular acne (TABLE 8).

In the 166 patients on whom follow-up observations could be made, 95 per cent were improved. As with all other locally applied steroids, the underlying eczematous condition tended to recur when therapy was discontinued, but the infection was adequately controlled. Several of these patients had previously reacted adversely to antibiotic–steroid combinations that contained neomycin.

The combination was prepared in Carbowax base, vanishing-cream base, and an aerosol spray. There was no significant difference in effects, but the vanishing-cream base seemed more acceptable to the patients than Carbowax, and the aerosol spray was especially effective over large or exudative areas and in the treatment of external otitis where the external canal was involved.

Most of the patients with pustular acne are adolescents who had been under therapy with sulfur-containing lotions and broad-spectrum antibiotics before starting the Triburon-Madribon regimen. With but few exceptions, the patients stated that they thought Madribon (one tablet daily) as effective as the antibiotic in controlling cystic lesions and pustules. Fifty-one of the sixty-two patients observed preferred Triburon-hydrocortisone ointment to the sulfur lotions previously used.

Summary and Conclusions

Triburon ointment, 0.1 per cent, is a safe and effective local treatment for pyodermas.

A combination of Triburon, 0.1 per cent, and hydrocortisone, 0.5 per cent, proved effective in 95 per cent of patients with secondarily infected eczematous eruptions.

Triburon-hydrocortisone ointment applied locally, and Madribon given systemically, are effective adjuncts in the control of pustular acne.

* Hoffmann-La Roche.

TOPICAL THERAPY IN ACNE VULGARIS

Seymour L. Hanfling
East Orange, N. J.

Acne vulgaris is still a major adolescent problem[1] despite the many recent remarkable advances in steroid and antimicrobial therapy. This is due to the extensive hormonal changes taking place at this age. It is known that even a relatively slight upset of the male-female hormone balance can produce acne. Whether this is the result of an undersecretion of estrogens or an oversecretion of the androgens[2] is immaterial, since the end result is the same. Despite the seriousness of the acne problem in many teenagers (Warshaw[3] found that 2 to 3 per cent of the 16- to 17-year olds with acne already had facial scarring), I do not feel that an attempt to remedy this hormonal imbalance is warranted. The process of growing up is so complicated that I believe nature must be given time to balance itself. As Sulzberger and Baer[4] have noted, the delicately adjusted hormonal mechanisms in adolescents often are functioning well in other respects, thus making unnecessary as well as undesirable the routine and widespread prescription of estrogenic substances. When nature fails, I step in, but not before. Not only has estrogen therapy often brought disappointing results,[5] but patients must be selected carefully for such therapy.[4, 6, 7] After all, most of us do not want to give estrogens to early teen-age girls. As to boys, I, for one, do not care to give female hormones to any young male. This, therefore, precludes an early attack on the primary cause of acne.

The secondary causes, however, must be investigated and any abnormalities remedied. Hypothyroidism,[1, 4] secondary anemia, A avitaminosis,[7] foci of infection,[8] and undue tensions must be corrected. Strict adherence to proper diet and complete avoidance of acnegenic foods such as nuts, chocolate, and iodides are imperative.

Other medication, systemic and topical, is directed toward reduction of comedones and control of infection. I prescribe internal antimicrobials for all moderately severe or severe pustular acnes to control the infection until other treatments take effect.

It had been my practice to prescribe these drugs by "feel," usually avoiding any drugs previously taken. Only in the very severe cases did I have a culture and antibiotic sensitivity testing performed. However, the culture and sensitivity tests undertaken in the present study (TABLE 1) revealed that many strains of cocci had become resistant to oral antimicrobials (I now understand why pustular acne of so many of my patients has failed to clear).

One other systemic treatment I use for all pustular acnes is a bacterial vaccine. For most cases, I use a stock vaccine containing staphylococci and streptococci plus their toxoids. For very severe cases, I use an autogenous vaccine.

Topical Therapy

In addition, I concentrate on the topical therapy of acne. In complete accord with Sulzberger,[9] I find that "despite the ever-growing importance of

TABLE 1
RESULTS OF CULTURES AND ANTIBIOTIC SENSITIVITY TESTING

	Case No.																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Aureomycin	G	G	G	G	G	G	G	G	M	M	M	G	G	G	G	G	G	G	M	G	M	M	—	G
Bacitracin	—	G	M	M	M	M	M	G	M	N	M	—	M	M	—	M	—	M	N	M	N	M	G	M
Chloromycetin	N	G	G	G	M	G	M	G	G	G	N	G	M	M	G	G	G	M	G	M	M	M	G	G
Erythromycin	G	M	G	G	G	G	M	G	G	N	N	G	G	G	G	G	G	M	N	G	N	M	—	G
Penicillin	N	G	N	G	G	N	G	G	G	N	N	N	N	G	N	N	G	G	M	G	N	N	—	G
Streptomycin	M	M	M	G	N	M	N	N	M	M	M	M	G	M	M	M	M	M	G	G	M	M	—	G
Terramycin	G	G	G	G	G	G	G	G	N	M	N	G	G	G	G	G	G	M	G	G	N	N	—	G
Tetracycline	G	G	G	G	G	G	G	G	N	M	N	G	G	G	G	G	G	M	G	G	G	N	—	G
Triburon	G	G	G	G	G+	G+	G−	G	G+	G	G	G	G+	G	G+	G+	G	G+	G	G	G	G	G	G
Furadantin	—	G	G	G	G	G	M	G	G	G	G	G	G	G	M	G	G	G	M	G	N	M	G	G

The organisms cultured in these sensitivity studies included hemolytic and nonhemolytic *Staphylococcus albus* and *Staph. aureus* (coagulase positive and negative), *beta-Streptococcus*, *Pseudomonas*, and para-colon bacillus.

Key: N, non-reactive; M, moderately reactive. Good reactions: G+, better than average; G, average; G−, slightly less than average.

the systemic medical approaches, the fortunate circumstance that potent and effective medicaments can be applied directly and repeatedly to the skin lesion itself still remains one of the mainstays of dermatology."

Beginning with the initial visit, I do "first things first," that is, careful incision of all pustules and expression of the contents (comedo plugs, pus, and sebum). Each is covered by a tiny Band-Aid upon which is placed a small quantity of an antimicrobial ointment. I then remove the comedo plugs and sebum in the uninfected papules, and finally express the comedones themselves. Eventually, I eliminate all the comedones present, leaving only the new plugs to contend with. At this point, the interval between visits is extended to the maximum that will allow me readily to clean up the new crop at each visit.

Beginning with the initial visit, when most of the time is spent in explaining the details of home topical therapy, treatment is aimed at the greatest possible reduction in comedo development. This is done because the comedo plug, acting as a cork, blocks the passage of the oil to the surface of the skin. Once this occurs, the result is a swelling filled with sebaceous material that readily becomes a culture medium for skin bacteria always present in the pores.

Since the comedo is the result of irritation of the follicular and duct opening due to excessive oil secretion, I begin my attack by removing the oil from the skin. For this I use Lowila Cake,* an effective detergent cleanser with a smooth lather. I prefer that it be used with a specially processed natural sea sponge. The involved areas are thoroughly washed with warm water and the Lowila Cake cleanser for 30 sec. 2 or 3 times daily. Cold water is used for rinsing. Any increase or decrease in the duration and frequency of the cleansing procedure is determined at each office visit and is based on the oiliness or dryness of the skin. If oiliness persists, Fostex Cake† is then recommended. When there are comedones of the ear and hairline, I recommend a new alcohol-acetone preparation. Few girls or even boys like to get suds in their hair and ears. Applied to cotton, this preparation cleans the hard-to-get-at areas and quickly evaporates. Many patients use this for the "quickie" clean-up when time is short or when they are fully clothed. It is especially useful in the extremely oily cases. Excellent responses have been seen in patients who used it on the entire face. In the simple keratotic comedo type of acne, I have found a new abrasive cleanser useful. Theoretically, if we can take off the top layers of the skin, we shall help remove all these tiny keratotic plugs. Here again, I have been wary of its use in all types of acne because of the possibility of aggravating the pustules, embedding the abrasive in the inflamed skin surrounding the infection, and excessive drying.

The patient is given specific instructions for cleansing the scalp as well as the face, chest, and back, because it is impossible to treat the face properly in the presence of an oily scalp. This requires detergent shampooing sufficiently often to prevent the scalp from becoming excessively oily. If there is no dandruff and a detergent shampoo is being used at least once a week, no

* Sodium lauryl sulfoacetate in a corn dextrin base, product of Westwood Pharmaceuticals, Buffalo, N. Y.

† A combination of wetting agents, soapless cleansers, hexachlorophene 1 per cent, micropulverized sulfur 2 per cent, and salicylic acid 2 per cent in cake form; product of Westwood Pharmaceuticals.

change in routine is advised. If dandruff is present, I recommend Fostex Cream.* This shampoo, used twice a week, leaves the scalp thoroughly clean, and clears all but the most persistent dandruff. Hair preparations containing oil are forbidden. For daytime use patients have the choice of any nonoily cosmetic foundation lotion, should they wish to use one. For nighttime use, I start them on a modified lotio alba which, by its oxidizing, astringent, and drying action, helps to prevent comedo formation.

Treatment of Infections in Acne

Most acne patients develop infections. It is most important that these infections be controlled quickly, since the larger the infection the larger the scar. For many years I had used a bacitracin-neomycin mixture in a petrolatum base applied on a Band-Aid in the office and prescribed for similar use at home each night. The greasy vehicle used by all manufacturers of this ointment left no choice but to have the patients wash their faces thoroughly and then apply this greasy ointment, which was not only cosmetically objectionable but therapeutically unsound. Since the recent availability of Triburon† ointment, a new broad-spectrum antimicrobial in a Carbowax base reported effective[10] against the organisms most frequently associated with acne, I have been using this preparation with excellent results in acne and superficial skin infections. Not only has it proved more effective than the bacitracin-neomycin mixture in controlling infection, but its less greasy base has been more acceptable. Although pustule formation is a continuing process, Triburon has been a great help in clearing any pustules present.

The reason for the superior effectiveness of Triburon can be seen by the results of the *in vitro* antibiotic sensitivity tests conducted on a series of skin infections, nearly 40 per cent of which involved acnes (TABLE 1). These tests were run at a hospital laboratory, using standard disks plus the Triburon disk containing 1.0 mg. of the chemical. The results show that *in vitro* no organisms were resistant to Triburon, whereas 90 per cent were resistant to bacitracin. From these test results, I believe that bacitracin is now practically useless for the local therapy of skin infections. Triburon, on the other hand, is both highly effective and more cosmetically acceptable. More recently this product has become available as Triburon Cream,‡ the same antimicrobial in a vanishing-cream base. Although my experience with this is very limited, it fulfills my criteria for a successful acne antimicrobial salve: minimum greasiness and maximum effectiveness against various skin bacteria.

Physical Therapy

While in the office, the acne patient is usually given a suberythema ultraviolet treatment. For some patients the dosage is increased enough to produce an erythema when it is thought that the skin will benefit from a mild peeling. It is well known that acne patients show tremendous improvement during the

* A combination of sodium lauryl sulfoacetate, wetting agent, hexachlorophene, micropulverized sulfur, and salicylic acid in cream form; product of Westwood Pharmaceuticals.

† An antimicrobial, triclobisonium chloride in a Carbowax and polyethylene base; product of Hoffmann-La Roche Inc., Nutley, N. J.

‡ An antimicrobial, triclobisonium chloride in a vanishing-cream base; product of Hoffmann-La Roche Inc.

summer following exposure to the sun, despite the increase in perspiration and skin oil secretion. Well-shielded X-ray therapy at a half-value layer of about 1.1 mm. of aluminum is still the best treatment in acne patients who are past 21 and who are not outgrowing the acne. Twelve to 16 quarter units at weekly intervals usually result in improvement and even clearing of the acne. The X-ray therapy actually inactivates the superficial oil glands sufficiently to reduce the patient's oil secretion to normal. I also use X-ray therapy on some of the older teen-agers who have not responded to other treatment and whose scarring is severe. In these cases, the aim is to prevent further scarring. Unfurtunately, X ray seems least effective where it is needed most, namely, in cases of acne conglobata.

Topical Hormone Therapy

The topical application of estrogen lotions has been recommended by some investigators, while others have found the results disappointing.[5] Theoretically, it should help considerably, especially in the male where internal estrogen therapy is not available. With each published report of successful estrogen therapy, I have tried the medication, but have found it to be completely ineffective.

As in all fields of medicine, the corticosteroids have a place in the topical treatment of acne by reducing the local inflammation present about the pustule. This medication is still very expensive and therefore cannot be prescribed routinely. Despite its cost, some of my patients are using it in a foundation-lotion base during the day and believe it to be helpful.

Dermabrasion

The final form of local therapy, necessary either when the patient has not started therapy soon enough or when it was not possible to prevent scarring, is dermabrasion. Usually scarring occurs when treatment is begun too late because, as is known, the patient who has followed an early and adequate long-term course of treatment does not become badly scarred. Facial planing (also called dermabrasion) is usually done after the acne subsides, but occasionally may be done when some pustules still persist. The primary purpose of the planing is to remove as much of the scar as possible. Healing takes 10 to 14 days, after which the skin slowly returns to normal. Since 1954, I have employed this procedure with considerable success.[11]

Conclusions

Much can be done for the acne patient; the sooner therapy is started, the better. Early intervention should be directed toward the reduction of comedo formation and the control of concomitant infection.

Systemic measures are useful, but must be reinforced with topical therapy. Antimicrobials, however, whether prescribed for internal or topical use should be administered discriminately. The alarming number of antibiotic-resistant strains seen in this series points to the need of bacterial sensitivity testing wherever possible, and the adequate use of new systemic and nonsystemic agents.

Experience with Triburon, a new topical antimicrobial, has been very encouraging. It has been more effective than bacitracin *in vitro* and superior to topical bacitracin-neomycin mixtures clinically.

Products for cleansing the skin such as Lowila Cake, Fostex Cake, and Fostex Cream help to reduce the formation of comedones, protecting the patient from permanent facial disfigurement.

Even when the skin has been scarred by neglect or by the severity of the infectious process, facial planing (dermabrasion) now makes it possible to improve the appearance of the skin.

References

1. Poirier, P. 1957. Acne and its treatment. Can. Med. Assoc. J. **77:** 866.
2. Robinson, M. M. 1959. Treatment of acne vulgaris with tetracycline, nystatin and tetracycline. Antibiotics Ann. 1957–1958. : 455.
3. Warshaw, T. G. 1958. Incidence of acne vulgaris. N. Y. State J. Med. **58:** 2797.
4. Sulzberger, M. B. & R. L. Baer. 1949. Acne vulgaris and its management. Year Book of Dermatol. and Syphilol. : 9–39.
5. Strakosch, E. A. 1959. A therapeutic study of pustular acne vulgaris. Antibiotic Med. & Clin. Therapy. **6:** 41–46.
6. Hypertrichosis and Acne (Questions and Answers). 1958. J. Am. Med. Assoc. **168:** 983.
7. Becker, F. T. 1953. The problem. Arch. Dermatol. and Syphilol. **67:** 173.
8. Andrews, G. C., A. N. Domonkos & C. F. Post. 1951. Treatment of vulgaris. J. Am. Med. Assoc. **146:** 1107.
9. Sulzberger, M. B. 1959. The choice of dermatologic drugs, drugs of choice. Antibiotics Ann. 1958–59. : 788–847.
10. Robinson, R. C. V. & L. E. Harmon. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. : 113–116.
11. Hanfling, S. L. & H. C. Goldberg. 1958. Rehabilitation by corrective surgical planing (dermabrasion). J. Med. Soc. New Jersey. **55:** 15.

Discussion

S. William Levy (*University of California, School of Medicine, San Francisco, Calif.*): Acne is basically a folliculitis, in which the follicle wall is inflamed and stimulated to keratin production. With its surrounding sebaceous glands the follicle is large, frequently lacks hair, and oils the skin. The comedo and whitehead are merely plugs of keratin composed of keratotic and parakeratotic material. As the follicle develops this enlarging plug, it loses its sebaceous glands, which eventually disappear as the plug becomes massive. Bacteria grow on and about the keratin plug and at its base. The blackhead and whitehead are keratin masses, therefore, which push out the epidermis and follicular epithelium, burrowing deeply into portions of the corium and becoming secondarily infected. White plugs on and about the nose are frequently a pure culture of the acne propion bacillus and not necessarily a keratin plug or whitehead. Possibly propionic acid is produced and is the responsible irritating agent in sebum which, in turn, undergoes a chemical change and irritates the skin in acnegenic persons. Perhaps the keratinous material, propionic acid, and/or bacteria break through this follicular wall, resulting in an irritative chemical reaction in the corium. The acne bacillus and other bacteria continue to proliferate aerobically and anerobically; possibly this is why systemic and topical antibacterial therapy is effective in controlling, but not necessarily stopping or preventing the process. In severe and moderately severe instances

of secondary bacterial infection in acne where scarring is a real possibility, systemic antibacterial substances certainly are indicated to control or alleviate the process. Such infection allows for residual scars that not only leave physical marks, but also result in mental changes in the personality. In mild and moderate acne where systemic antibacterials are contraindicated or not necessary, topical antibacterial substances may be of benefit. I agree with S. L. Hanfling in the use of antibacterial substances topically in acne, and in more than a few instances I have seen encouraging responses. I would like to see a double-blind control study in this regard. Resistant bacterial strains are real, but when scarring from infection in acne is a true possibility such realities can be ignored temporarily. Anyone who has seen chronic acne, facial scarring, or an acute facial infection certainly can realize what a psychological barrier this defect may be.

In a brief preliminary clinical trial of topical Triburon in acne, I have found it to be of equal benefit as compared with other topical antibacterial substances. Although no sensitivity reactions to the substance have been seen on topical application to more than 100 patients, doubtless with extended usage a few instances of topical sensitivity can be expected. Its advantages are basically lower cost, infrequent resistance to bacteria, and infrequent topical reactions as compared with neomycin and bacitracin, and availability in either a water-miscible Carbowax base or a drying vanishing-cream base. It can be used for the inflammatory types of adolescent acne, and is available in combination with hydrocortisone.

Whether adolescent or young-adult acne is a multifaceted hormonal, genetic, stress, alarm, or adaptation reaction on the part of a given individual is immaterial in this discussion. The one point of importance, however, is that we now have topical and systemic antibacterial agents that can control partially the activity and prevent scarring. These agents should be used where indicated, and can be used relatively safely over an extended period of time. They can help prevent the psychological misfits and the personality changes seen in former years as a result of persistent acne activity with scarring.

THE USE OF TOPICAL ANTIBACTERIALS IN SURGICAL PROCEDURES*

Richard D. Floyd and William G. Anlyan
Department of Surgery, Duke University Medical Center, Durham, N. C.

A synthesized bisquaternary compound, triclobisonium chloride (Triburon†), is a topical antibacterial. It is available as an ointment (0.1 per cent concentration Carbowax) for local application or in a 10 per cent solution that can be diluted with saline for compresses. This antibacterial agent has been shown to exert high bacteriostatic and a moderate bactericidal activity against Gram-positive and Gram-negative organisms *in vitro*. It has marked local antibacterial effect against *Streptococcus hemolyticus* and *Staphylococcus aureus in vivo* regardless of their resistance to antibiotics.[1]

The purpose of this paper is to present our clinical experience with Triburon therapy in general surgical infections and surgical dressings.

Method

This study was carried out on 100 surgical patients. The patients in this series were divided into 3 groups on the basis of the type of wound to be treated: (1) surgically dressed, clean operative incisions; (2) open or dressed contaminated operative incisions; and (3) superficial infections unrelated to an operative procedure (TABLE 1). Some of the superficial infections were drained as indicated clinically. The contaminated incisions were either partially closed or left open. Photographs and cultures were taken in patients with superficial infections and operative wound infections before treatment and, when feasible, posttreatment cultures and photographs were repeated. All the clean operative incisions were covered with a thin layer of the ointment immediately prior to applying a sterile gauze dressing. The superficial infections and contaminated incisions were treated 3 times daily for 1 hour with either direct application or with compresses of 10 cc. of Triburon chloride solution in 1000 cc. of saline.

Results

Fifty patients with clean surgical incisions treated with Triburon ointment revealed no superficial or deep subcutaneous infections in contrast to a 2.3 per cent infection rate in a control group of clean wounds at the Durham Veterans Administration Hospital, Durham, N. C., where Triburon was not used.

In the Triburon-treated cases the following occurred. In one patient, a large, noninfected hematoma was evacuated, and the wound healed without infection. Another patient with a low anterior colon resection drained material containing *Proteus vulgaris* on culture; however, the skin incision was not involved. These operative incisions were usually redressed between the sixth and eighth postoperative days. No maceration or redness of the skin was observed in any of the patients.

* The study reported in this paper was supported by a grant-in-aid from Hoffmann-La Roche Inc., Nutley, N. J.

† Hoffmann-La Roche.

Twenty-five patients with superficial infections were treated either with compresses or with ointment application, depending on the nature of the infection. The duration of treatment varied from 1 application of the ointment to a 3-week period of treatment by either the ointment or compresses. The response of the uncomplicated infected superficial wounds was excellent in more than 90 per cent (19) of the cases treated. In 2 patients a fair-to-good response was observed. Four patients had either minimal or no response to the treatment.

Of 25 patients with contaminated operative incisions, the majority with rectal procedures, 72 per cent were contaminated with coliform organisms. Two

Table 1
Wounds Treated in Study of 100 Patients

Noncontaminated wounds (operative incisions)	Superficial wounds (infected)	Contaminated wounds (operative incisions)
Neck incisions	Furuncles	Pilonidal excisions
Laparotomy incisions	Carbuncles	Hemorrhoidectomies
Thoracotomy incisions	Pyoderma gangrenosum	Excisions of fistula and fissure-in-ano
Hernia incisions	Ingrown toenail	Colostomies
Extremity incisions	Infected cold injury	Amputation, secondary closures
	Infected abrasions	Postoperative infection in radical mastectomy
	Infected insect bites	
	Ulcers of upper and lower extremities	
	Infected snake bite	
	Hydradenitis	
	Abscesses of leg	
	Infected stab wound	
	Subungual infection	
	Lacerations	

Table 2
Major Organisms of Infected and Contaminated Wounds

Str. hemolyticus
Staph. aureus and *albus*
P. vulgaris
Escherichia coli (other coliforms)
Pseudomonas aeruginosa

patients in this group who failed to respond to treatment were cases of postoperative break down of secondarily closed amputation stumps. However, these patients had arterial insufficiency, and higher amputations were necessary. *P. vulgaris* and *Staph. aureus* were the offending organisms in both patients.

Discussion

One of the major problems in using topical antibacterial agents has been local reaction and the possible risk of producing sensitivity to antibiotics that would prevent future oral or parenteral use. In extensive patch tests and sen-

sitivity studies, Triburon was found to cause undesirable reactions in less than 1 per cent of the patients.[2, 3]

Today many surgeons prefer to use dry dressings on clean operative wounds for the first 48 to 72 hours. Whereas Vaseline application to the incisions often resulted in maceration of the skin, no such maceration occurred with a light application of Triburon, which also prevented bacterial growth in the region of the surgical incision.

The use of Triburon compresses after surgical drainage of perirectal abscesses and after opening or excision of fistulae-in-ano was quite effective in reducing bacterial flora and promoting tissue granulation. The use of a small amount of Triburon ointment on rectal packs following hemorrhoidectomy has also been equally effective.

In cases of pyoderma gangrenosum, infected ulcers on extremities (in patients with Buerger's disease), and in stasis ulcers secondarily infected with *Staph. aureus*, only minimal change was noted on application of compresses or ointment. These chronically infected wounds in patients with systemic disease were markedly resistant to any type of therapy.

Organisms cultured from the superficial infections and contaminated incisions are listed in TABLE 2.

In the 100 cases, no local or systemic reaction to Triburon application was observed.

Conclusion

Triburon applied in clean primarily closed surgical incisions, in superficial infections, and in contaminated surgical incisions resulted in no local or systemic reactions in 100 cases. In clean surgical wounds the incidence of wound infections in the Triburon-treated group was 0 per cent in contrast to a 2.3 per cent rate in the untreated control group. Triburon was effective in treating superficial infections and contaminated surgical wounds.

The results of treatment with Triburon were comparable to those obtained with topical antibiotic agents currently available, without the sensitivity phenomena associated with the use of the latter.

References

1. SCHNITZER, R. J., E. GRUNBERG, W. F. DELORENZO & R. E. BAGDON. 1959. Triclobisonium chloride (Triburon), an antimicrobial agent with local activity in living host tissues. Antibiotics & Chemotherapy. **9**: 267–276.
2. EDELSON, E., E. GRUNBERG & T. V. MORTON 1959. Clinical appraisal of a new topical quaternary compound Ro 5-0810/1. Antibiotics Ann. 1958–1959. : 110–112.
3. ROBINSON, R. C. V. & L. E. HARMON. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. : 113–116.

THE USE OF TRICLOBISONIUM CHLORIDE (TRIBURON*) IN PLASTIC SURGERY†

N. Georgiade, K. Pickrell, F. Morris

Division of Plastic and Maxillofacial Surgery, Duke University Medical Center, Durham, N. C.

There is a constant need for an effective topical bacteriostatic, bactericidal, or antimicrobial agent incorporated in a vehicle suitable for reconstructive surgical procedures. Varying degrees of success have been attained in the past with potent bacteriostatic and bactericidal agents in water-soluble and nonwater-soluble bases. A newly synthesized antimicrobial agent, triclobisonium chloride (Triburon), a bisquaternary diamine derived from beta-ionone and shown to exert a high bacteriostatic and moderate bactericidal activity against a wide range of Gram-positive and Gram-negative organisms *in vitro*,[1] has been utilized in this clinical study.

In the past 16 months triclobisonium chloride (0.1 per cent in a water-soluble Carbowax base), incorporated in gauze and autoclaved, has been used as a dressing material in more than 250 reconstructive procedures. These included uses on donor areas, following the obtaining of split-thickness skin grafts; on first-, second-, and third-degree burn areas; on split- and full-thickness grafts; in postdermabrasion procedures; as well as in dressings over skin flaps and granulating areas.

Whenever practicable, this antimicrobial agent was compared segmentally with another generally accepted dressing material—namely, nitrofurazone (Furacin)—with 1 area in the same location being dressed with each of these ointments. The triclobisonium chloride had an immediate advantage when used in exposed areas because it is a colorless ointment and did not stain the overlying gauze, making it more cosmetically acceptable. Approximately 5 per cent of the patients were found to be sensitive to the above-mentioned comparative ointment, as evidenced by mild to severe localized or generalized erythema and blistering. Redressing these same sensitized areas with triclobisonium chloride produced no evidence of sensitivity.

Clinical Procedures

Donor areas. Following removal of a suitable split-thickness skin graft, the donor areas were allowed to clot and were then dressed with a single layer of triclobisonium chloride–impregnated gauze and subsequently covered with a sterile bulky dressing. On the first postoperative day the donor area was exposed down to the original single triclobisonium chloride–impregnated gauze layer (FIGURE 1). This layer was allowed to remain undisturbed and a cradle was then placed over the patient's bed allowing the donor area to remain exposed for maximum drying without contact with the surrounding sheets and clothing. In 7 to 10 days this single layer of gauze became loosened and was gradually trimmed as it became detached. As the dressing loosened, the underlying donor area was found to be pink and completely epithelialized.

* Hoffmann-La Roche.

† The study reported in this paper was supported by a grant-in-aid from Hoffmann-La Roche Inc., Nutley, N. J.

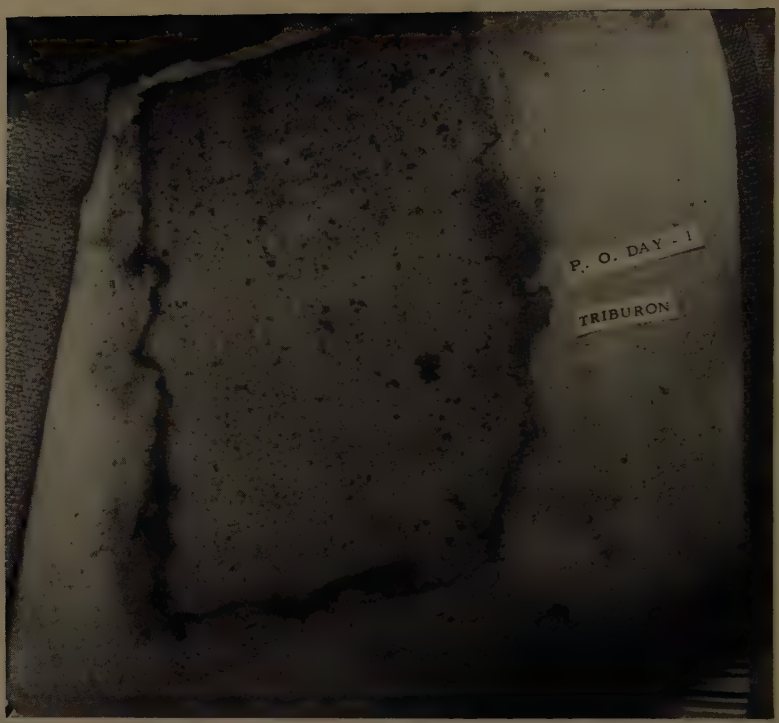


FIGURE 1. Appearance of donor area on first postoperative day following removal of overlying dry dressing.

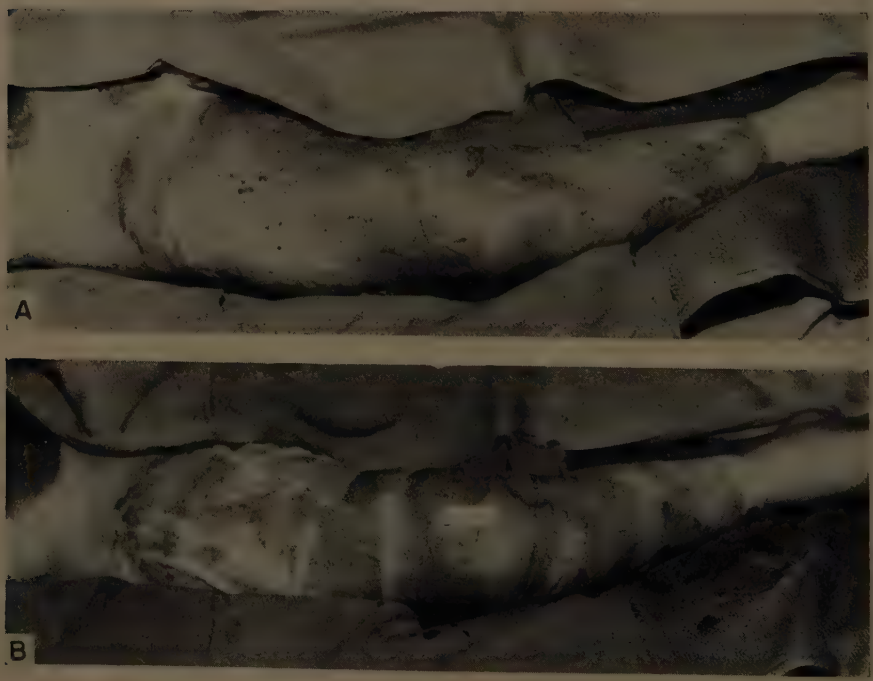


FIGURE 2. First- and second-degree burns of lower extremity dressed with Triburon ointment impregnated in layers of sterile gauze.

FIGURE 3. (*a*) Third-degree burns of lower extremity, with granulation formation previously dressed with triclobisonium chloride–impregnated gauze and ready for grafting. (*b*) Appearance of grafted areas covered with Triburon gauze. (*c*) Stamp grafts applied to extensive burned areas prior to application of Triburon gauze.

Burns. First- and second-degree burn areas were first cleaned with a skin antiseptic, and any blisters present were aspirated. The burned areas were then covered with a triclobisonium chloride–impregnated gauze reinforced with sterile gauze sponges and stockinette cut on the bias.[2, 3] The dressings were

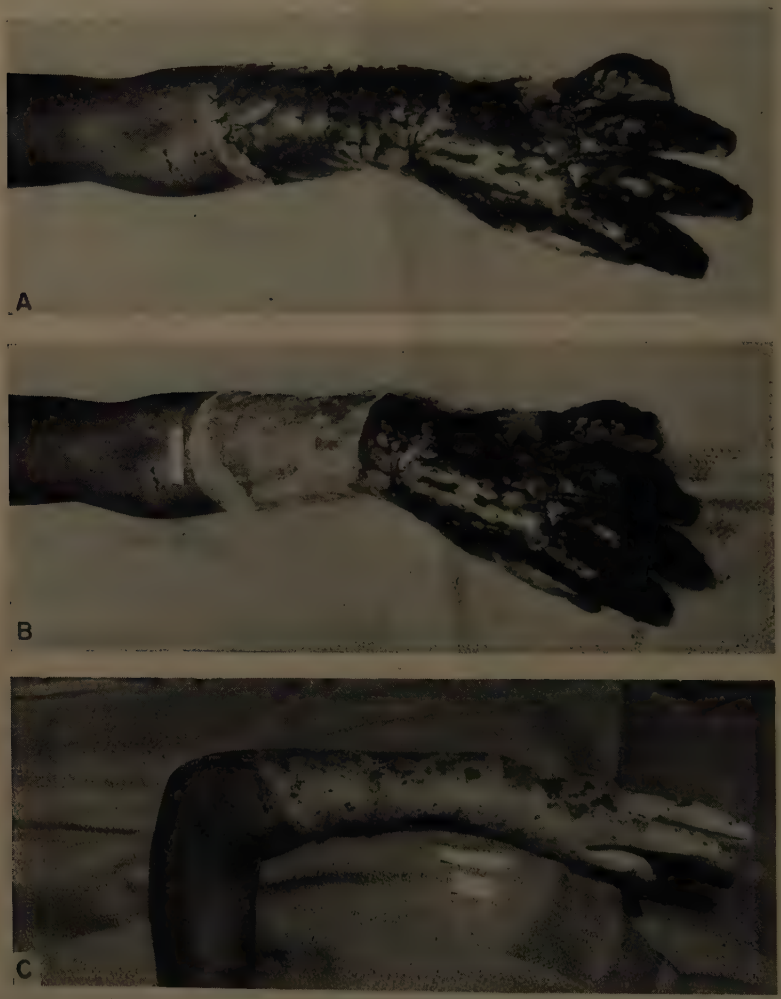


FIGURE 4. (*a*) Split-thickness skin grafts applied to third-degree burns of hand. (*b*) Triburon-impregnated gauze dressing applied over skin grafts. (*c*) Nine days after grafting.

allowed to remain intact for approximately 6 days, depending on the condition of the areas dressed. Examination of the superficially burned areas revealed uneventful healing, and further dressings were discontinued. For the deeper second-degree burn areas triclobisonium chloride gauze was reapplied as described above for an additional 3 to 4 days before re-evaluation of the burned area was made (FIGURES 2 and 3).

Third-degree burn areas were dressed initially the same as the burns of

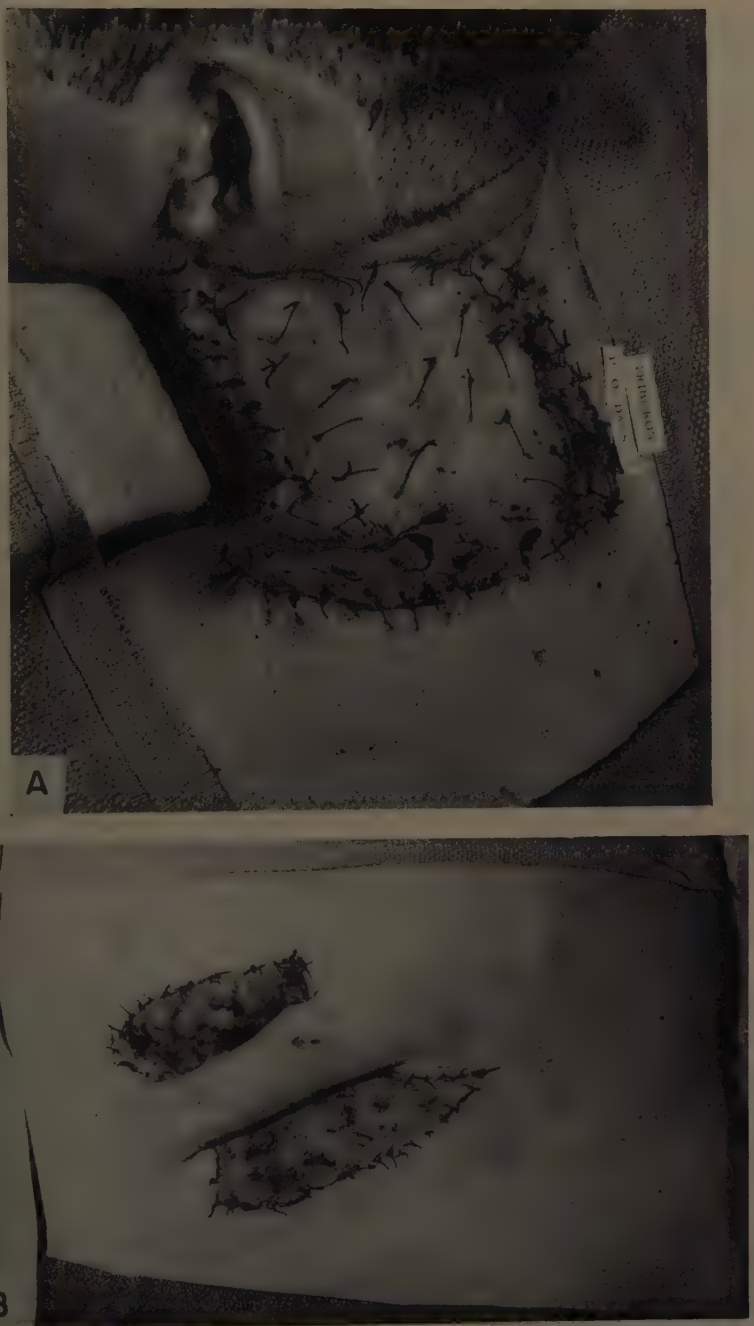


FIGURE 5. (*a*) Operative defect of neck resurfaced with a split-thickness skin graft and dressed with Triburon. Eight days after grafting. (*b*) Five days after elevation of an abdominal tube and split grafting of underlying donor area, with Triburon gauze dressing over graft.

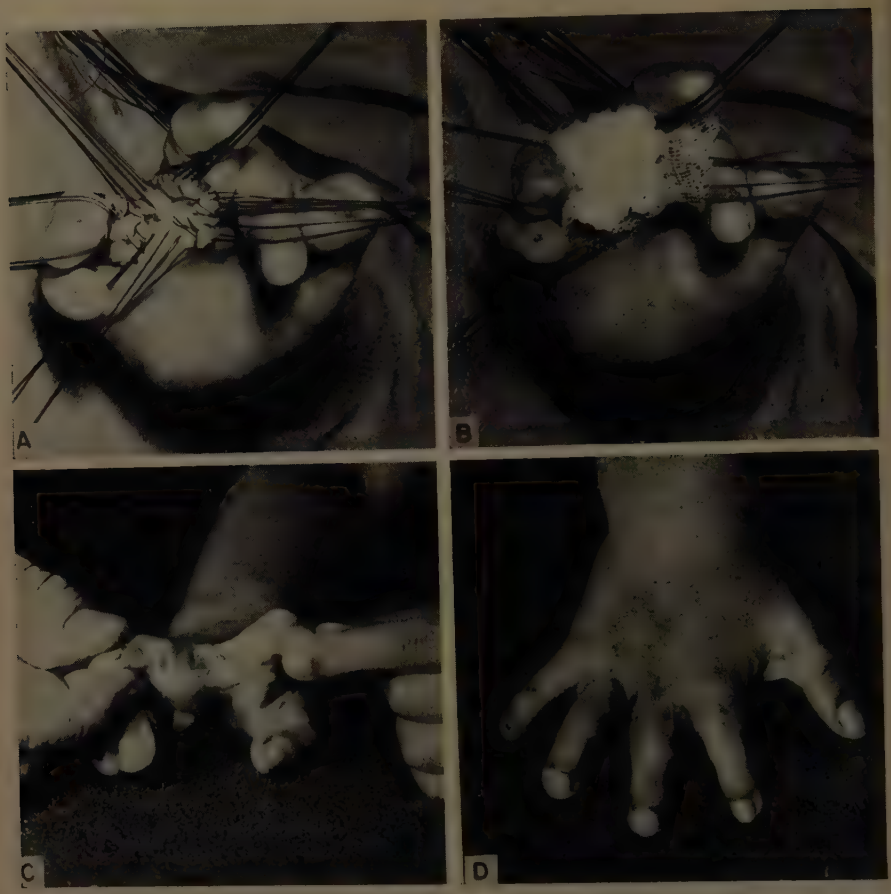


FIGURE 6. (*a*, *b*) Appearance of full-thickness grafts prior to and following dressing with Triburon gauze and bolus. (*c*, *d*) Nine days after grafting.

FIGURE 7. (*a*, *b*, *c*) First, fifth, and eighth postoperative days following dermabrasion to entire face and dressing with Triburon gauze.

FIGURE 8. (*a*) Large sacral decubitus ulcer prior to closure. (*b*, *c*) Transfer of large buttocks flaps with split-grafting and dressing of grafted area with Triburon-impregnated gauze.

lesser degree; however, as the necrotic tissue became separated from the deeper underlying tissues and these areas formed a granulating base, the ointment gauze was replaced with a dry sterile gauze a few days prior to anticipated resurfacing. This gauze was changed daily in order to maintain the area as a flat dry base, suitable for resurfacing with split-thickness skin grafts.

Newly skin-grafted areas. Split-thickness skin grafts applied over granulating areas, as in third-degree burns, were covered with triclobisonium chloride-impregnated gauze and sterile bulky dressings, with immobilization of the newly grafted areas (FIGURE 4). Redressing of the split-thickness skin-graft areas was performed on the fourth day and usually every other day until healing was completed. When areas were covered with "stamp" grafts, a similar procedure was carried out (FIGURE 3).

In clean surgical defects resurfaced with split-thickness skin grafts the initial redressing was not carried out until the seventh postoperative day (FIGURE 5).

Full-thickness skin grafts were always placed on clean surgical wounds, dressed with triclobisonium chloride–impregnated gauze, immobilized, and not redressed until the seventh postoperative day (FIGURE 6).

Dermabrasion procedures. Following the use of the rotary abrasive wheels or steel wires for abrading scarred facial areas, areas were copiously irrigated with sterile saline and then covered with a single layer of triclobisonium gauze. This single layer was reinforced with superimposed dry sterile dressings. On the first postoperative day all the overyling dressings were removed with the exception of the triclobisonium chloride–gauze layer directly over the abraded areas. During the ensuing 5 to 7 days the gauze, initially quite adherent, gradually loosened as healing proceeded uneventfully underneath. The loose gauze was trimmed daily, revealing a well-healed pink epithelium (FIGURE 7).

Miscellaneous. Routine scar revision, Z-plasties, flaps, lacerations, and denuded areas were covered with a single layer of triclobisonium chloride–impregnated gauze. No instance of sensitivity was noted. In contaminated areas containing *Escherichia coli* or *Pseudomonas aeruginosa*, (as shown on bacteriological study)[4] use of this gauze appeared to have no affect on the growth of the contaminating agents (FIGURE 8).

Summary and Conclusions

A new potent antimicrobial agent incorporated in a water-soluble base has been used topically without any evidence of sensitivity or other untoward local or systemic effects, although as much as 30 per cent of the body surface had been covered at one time with this material. The agent has been used in more than 250 general plastic and reconstructive surgery procedures, with satisfactory results.

References

1. SCHNITZER, R. J., E. GRUNBERG, W. F. DELORENZO & R. E. BAGDON. 1959. Triclobisonium chloride (Triburon), an antimicrobial agent with local activity in living host tissues. Antibiotics & Chemotherapy. **9:** 267–276.
2. MOWLEN, R. & R. L. DAWSON. 1954. Management of burns. I. The recent burn, first aid treatment. Lancet. **1:** 39.
3. PICKRELL, K., N. GEORGIADE, H. CRAWFORD & C. MAGUIRE. 1956. General principles in the treatment of burns. Postgrad. Med. **20:** 26.
4. ZINSSER, H. & S. BAYNE-JONES. 1937. A Text Book of Bacteriology. Appleton-Century. New York, N. Y.

CLINICAL EXPERIENCE WITH A NEW ANTIBACTERIAL IN PROCTOLOGIC PRACTICE

George L. Becker
Paterson, N. J.

There is hardly a disorder of the anorectal region that may not at some time require treatment for the prevention or control of infection. Constant local irritation from leukorrhea, daily use of toilet soaps, and retention of fecal remnants are only a few of the factors that render this area susceptible to infection and prolong the course of existing pathology. If prevention and control of infection can be accomplished with a topical agent, many of the undesirable effects of systemic therapy can be avoided. This is also true when corticosteroids are indicated in conjunction with antibacterials. In the evaluation of any topical antibacterial for proctologic use, several factors must be considered. Briefly, these include: noninterference with wound healing (particularly for postoperative care), lack of sensitivity for allergic reactions, nonirritation, and cosmetic acceptability. Routine topical and systemic use of broad-spectrum antibiotics is ill advised as they often sensitize the patient, thus depriving him of their life-saving benefits at a later date, initiate pruritus in the anorectal region, and predispose him to moniliasis.[1]

This investigation is concerned with a new topical microbicide, Triburon, in combination with 0.5 per cent hydrocortisone.* Reports on Triburon[2, 3] have shown it to be both effective and safe, producing no evidence of irritation or sensitization in one study, and only one case of irritation in another. The results observed in superficial infections indicated the usefulness of Triburon in proctologic practice. Initially, I intended to limit my trial of the drug to the postoperative care of perianal wounds. However, following successful and safe results in this area, I extended the study to include one group of patients whose chief complaint was pruritus ani and to still another group with postanal fissure.

Methods and Material

Group I consisted of 26 postoperative cases. The indications for surgery included fissures, fistulas, hemorrhoids, and combinations of these. All patients received the conventional postoperative treatment of sitz baths and Burrow's and Bradosol wet dressings for 4 to 5 days postoperatively while the patient was still hospitalized. Subsequently, Triburon with hydrocortisone ointment was prescribed. The duration of treatment ranged from 4 days in one patient to 5 weeks in another in whom rectal wounds were complicated by monilial infestation. Most patients received the medication for from 1 to 3 weeks before and after bowel movements and at night using a cotted finger. When healing became sluggish, an antibiotic or other germicidal ointment was used.

Group II consisted of 34 patients whose chief complaint was pruritus ani, often complicated by vaginitis. The diagnostic categories included: mycin dermatitis, neurodermatitis, endocervicitis vaginitis, keratolytic infection,

* Hoffmann-La Roche.

allergy desquamation, and monilial infection of the vaginal and perianal regions. Previous treatment included the usual medications, that is, potassium permanganate wet dressings, antibiotics, Phisohex, Burrow's, Myconef and Vioform. Triburon was applied to the anal area before and after bowel movements and at night. The patients with vaginal infections were instructed to use the ointment vaginally as well as topically following a cleansing douche at night. The duration of treatment was from 6 to 42 days.

Group III, consisting of 8 patients with anal fissures of varying degree from subacute to acute, were treated with Triburon together with the usual fissure regimen for from 7 to 14 days.

TABLE 1

RESULTS OF TRIBURON PLUS HYDROCORTISONE THERAPY IN PROCTOLOGIC DISORDERS

Indications	No. patients	Duration of therapy		Results		Side effects
		Average (days)	Range (days)	Effective	Unsatisfactory	
Group I Postoperative care of perianal wounds	26	17	4–35	23 (88.5%)	3	1 (Slight pruritis)
Group II Pruritus ani*	34	21	6–42	33 (97.1%)	1	1 (Mild reaction)
Group III Postanal fissures	8	10	7–14	6 (75%)	2	1 (Irritation)

* Complicated by vaginal and perianal infections and dermatitis in most cases.

Results

Group I (TABLE 1): the response was classified as good or satisfactory in 23 of the 26 postoperative cases (88.5 per cent) with healing of the wound progressing very well up to 2 weeks. Except for 4 female patients who developed monilialike infections, healing was excellent with less scarring, without pus formation, and with greater comfort to the patient than had been noted in the past with a variety of other medications. Pruritis ani, frequent and annoying in the later stages of postoperative healing, was not encountered in this series.

In Group II (TABLE 1) application of Triburon locally, as well as vaginally when necessary, effected good results in all but 1 of the 34 patients with pruritis ani. One patient with mycin dermatitis had a reaction to Triburon following 2 weeks of treatment. This was rapidly relieved upon discontinuance of therapy. In 2 patients who exhibited a good response after 4 and 5 weeks of therapy, symptoms recurred following cessation of medication. The most dramatic response was observed after treatment (6 days in one case and 1 month in another) in 8 patients with mixed vaginal and proved monilial infections.

Group III (TABLE 1): good results were obtained in 6 of 8 patients with postanal fissure, the duration of treatment for complete relief of symptoms being

7 to 14 days. In one patient, treatment was interrupted because of irritation. Examination revealed a low-grade dermatitis of undetermined cause.

Discussion

Despite the fact that medical management of anorectal disorders has been substantially enhanced by a number of systemic drugs (sedatives, antihistamines, and tranquilizers), the principal and immediate relief is obtained from local applications[4] designed to control infection and reduce inflammation. Among the objectives in postoperative care of perianal wounds, prevention of infection and rapid uncomplicated healing are paramount. With this in view, the proctologist is ever on the alert for a nonirritating antibacterial agent that can be used conveniently and effectively in this area. From our preliminary observations with Triburon hydrocortisone ointment, it is felt that these objectives have been attained. Not only was healing impressive, but the comfort afforded the patient is a highly significant factor in such conditions.

As might be expected, Triburon with hydrocortisone was effective in the treatment of pruritus ani. Since hydrocortisone is generally considered to be one of the greatest advances in the management of pruritus ani[5-7] its inclusion with an antibacterial such as Triburon is rational. When we consider that bacterial and mycotic infections frequently are involved in pruritus ani,[8, 9] as was the case in the present series, and that inflamed skin exhibits reduced antibacterial powers against pathogenic organisms, the results obtained with this combination are undoubtedly superior to what might be expected with either agent alone.

It is significant that no adverse systemic reactions were noted in any of the patients treated. This confirms previous observations that absorption of hydrocortisone is not of sufficient magnitude to be of significance systemically, and indicates that Triburon is apparently slowly or incompletely absorbed. The minimal occurrence of side effects encountered in this evaluation does not represent a statistically valid incidence in such a small group, but compares favorably with previously used agents.

Frequent involvement of the genitalia as well as anorectal areas points to the need for medical attention to this region. Our practice of treating the patients both vaginally and perianally has increased considerably the response to therapy.

Summary

Triburon with hydrocortisone, a new broad-spectrum topical antibacterial-antipruritic ointment, has been clinically evaluated in 68 proctologic patients: 26 postoperative, 34 pruritus ani (often complicated by vaginal and perianal infections), and 8 anal fissures.

This agent was found effective in 91.2 per cent of the 68 patients, the highest degree of efficacy occurring in cases of pruritus ani (97.1 per cent). In this group 8 cases of monilial infestation responded dramatically.

In postoperative care of perianal wounds, healing was excellent. There was less scarring and no pus formation.

An extremely low incidence of side effects was observed in this series.

Based on these preliminary observations, I consider Triburon to be a safe topical antibacterial agent that merits further investigation for delineation of the precise indications in proctologic practice.

References

1. Becker, G. L. 1958. Management of perianal dermatoses. Diseases Colon and Rectum. **1:** 345.
2. Edelson, E., E. Grunberg & T. V. Morton. 1959. Clinical appraisal of a new topical quaternary compound, Ro 5-0810/1. Antibiotics Ann. 1958–1959. : 110.
3. Robinson, C. V. R. & L. E. Harmon. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. : 113.
4. Steigman, F. & E. Broccolo. 1958. Medicinal therapy of anorectal disorders. Med. Times. **86:** 1212.
5. Fromer, J. L. 1955. Dermatologic concepts and management of pruritus ani. Am. J. Surgery. **90:** 805.
6. Robinson, M. M. 1958. Anogenital pruritus. Am. J. Proctol. **9:** 361.
7. Wilson, C. C. 1959. New treatment for pruritus ani. Southern Med. J. **52:** 96.
8. Leifer, W. 1955. Pruritus ani. Surg. Clin. North Am. **35:** 1479.
9. Brossy, J. J. 1955. Pruritus ani. Proc. Roy. Soc. Med. **48:** 499.

THE CONTROL OF INFECTION IN BURN THERAPY

Jerome Gelb
Kessler Institute for Rehabilitation, West Orange, N. J.

It is essential to remember that a burn is an open surgical wound that is highly susceptible to infection, and that if measures to control infection are not instituted, healing may be hopelessly delayed. Anyone treating burns is aware of the destruction of tissue that results following infection, the time and energy involved in treatment, and the severe morbidity and high mortality. While it is not within the scope of this paper to discuss the advantages and disadvantages of the exposure and occlusive-dressing methods, it should be noted that the primary aim of local care—namely, prevention of further contamination and reinfection—can be accomplished by either technique, if properly used. However, we see a great many infected burns that have been treated by both methods. Regardless of the method used, the need for proper attention to the wound itself remains. The patient is often given supportive and replacement therapy without the necessary local wound care. Thus, an exposed or occluded wound becomes a neglected wound. Whatever method is employed, thorough surgical and mechanical cleansing is imperative.

Reports of the successful treatment of wounds and burns with triclobisonium chloride encouraged us to employ this medication in the burn cases seen in a general and a specialized hospital. Its broad antimicrobial spectrum and nonadherent base seemed to endow it with special value for this purpose.

Materials and Methods

Ten consecutive burn cases seen in hospital were treated with Triburon. The wounds had resulted from first-, second- and third-degree burns—some minor and others of a critical nature. The late burns were seen initially for the purpose of grafting and were not in a suitable state for such surgery. Nine of the patients were seen 2 days to 5 weeks after the burn trauma, and one 6 months after.

Triburon, 0.1 per cent, was impregnated in fine-mesh gauze and placed directly on the burn wound. The ointment was also applied to all graft donor sites. In most instances, dressings were done daily under sterile conditions in a dressing room. In critical burns, where anesthesia was required, dressings were applied 2 to 3 times weekly in the operating room. In the latter cases, the ointment was heavily spread over the wound surface. All but 1 patient, treated at home, received systemic antibiotics. Replacement therapy was administered where required, and the surgical treatment varied according to the severity of the wound. Bacterial studies made of each wound revealed the following organisms: hemolytic and nonhemolytic *Staphylococcus aureus*, *Escherichia coli*, *Aerobacter aerogenes*, and *Pseudomonas pyocyanea*.

The case reports below are cited as representative of the severity of the burn prior to therapy and of the absence of infection and suppuration in all cases following treatment.

Case Reports

Case 1. A 58-year-old female diabetic sustained a puncture wound of the right forearm. To alleviate pain and swelling she had applied hot compresses that resulted in second- and third-degree burns of the hand and forearm. The patient, seen 5 days after injury, had acute suppurative wounds. Bacteriological cultures revealed *Staph. aureus*. Triburon dressings were applied daily. The wound improved and was ready to accept a skin graft. At the end of 6 days, wound culture revealed no organisms (FIGURE 1).

Case 2. A 53-year-old female sustained hot-water burns on the right hand. She was seen initially 5 weeks after the burn trauma. Bacteriological culture revealed *E. coli*, hemolytic *Staph. aureus*, and *A. aerogenes*. Daily application of Triburon dressings for 6 days resulted in excellent wound improvement, making grafting possible within 1 week.

Case 3. A 34-year-old male sustained burns of the right thigh, leg, foot, chest, arm, and hand as a result of an airplane crash. Burns involved approximately 25 per cent of body surface. The patient was initially seen 3 weeks after the accident. A bilateral leg amputation had been done and the patient still had wounds on the chest and hand. The culture revealed *Staph. aureus* and *Ps. aeruginosa*. Triburon dressings were applied daily in preparation for grafting. Grafting of stumps was possible after 5 days of treatment with Triburon. No infection or suppuration was noted.

Case 4. A 30-year-old male sustained electric burns on both upper extremities by contact with a high-tension wire. He was seen 5 days after burn trauma. Organisms cultured included Gram-positive cocci and bacilli and Gram-negative bacilli. Free spores were also present. Therapy consisted of multiple incisions and application of Triburon dressings. When infection was controlled, amputation of both arms was performed. Stumps showed no infection and healed well. Daily application of Triburon was continued through 3 periods of grafting (FIGURE 2).

Case 5. A 34-year-old male sustained second- and third-degree burns of the face, arms, forearms, thighs, legs, and back. Approximately 45 to 50 per cent of the body surface area was involved. The patient was seen 72 hours following the acute trauma in electrolyte imbalance. *Ps. pyocyanea* were cultured. Following replacement therapy, Triburon-impregnated gauze was applied in the operating room twice a week under general anesthesia. Throughout the course, the wound surface remained free of suppuration and appeared ready to accept grafts. However, on the eighteenth day after the burn was incurred the patient died of mesenteric thrombosis.

Case 6. A 65-year-old female with second- and third-degree burns of the abdomen, thighs, and left mammary region was seen 16 days after trauma. Approximately 15 per cent of the body surface was involved. Bacterial cultures revealed nonhemolytic staphylococci. Surgical excision of the necrotic tissues was performed, and after 3 or 4 daily dressings of Triburon there was regeneration of the epithelial linings of hair follicles and sweat glands. Only 2 small grafts to the right thigh were required (FIGURE 3).

Case 7. A 31-year-old female nurse sustained second-degree burns of the mammary region when removing sterile goods from an autoclave. She was

FIGURE 1. (*a*) Second- and third-degree burns of hand (with vesicles and suppuration) 5 days after injury; extensor tendons exposed. (*b*) Granulation tissue over extensor tendon 2 weeks after daily Triburon dressings; wound is ready to accept skin graft. (*c*) Complete healing as a result of skin graft.

seen immediately; treatment consisted of mechanical cleansing and the application of Triburon-impregnated fine-mesh gauze for 2 weeks, at home. Complete healing was observed in 2 weeks.

Case 8. A 30-year-old male sustained burns of hands, forearms, thighs, and legs in an explosion. Approximately 25 per cent of the body surface was

FIGURE 2. (*a, b*) Electric burns of both hands, forearms, arms, and axillae 5 days after burn trauma; appearance of dry gangrene on arms and forearms. (*c, d, e*) Bilateral arm amputations and surgical excision of eschar; open wounds treated with Triburon-impregnated gauze in preparation for revisions of stumps and skin graft. (*f, g, h*) Skin grafts to both axillae and revisions of stumps after local Triburon therapy; uneventful healing of wound.

burned. *Ps. pyocyanea* were cultured. Triburon was applied to wounds twice a week in the operating room, starting 3 days after the burn was incurred. No infection or suppuration was noted, and 2 grafting procedures were performed successfully (FIGURE 4).

Case 9. A 34-year-old paraplegic female was first seen 3 weeks after onset of third-degree burns of toes and right foot sustained on a hot stove. Eschar formation had resulted. Surgical excision of the eschar was performed and

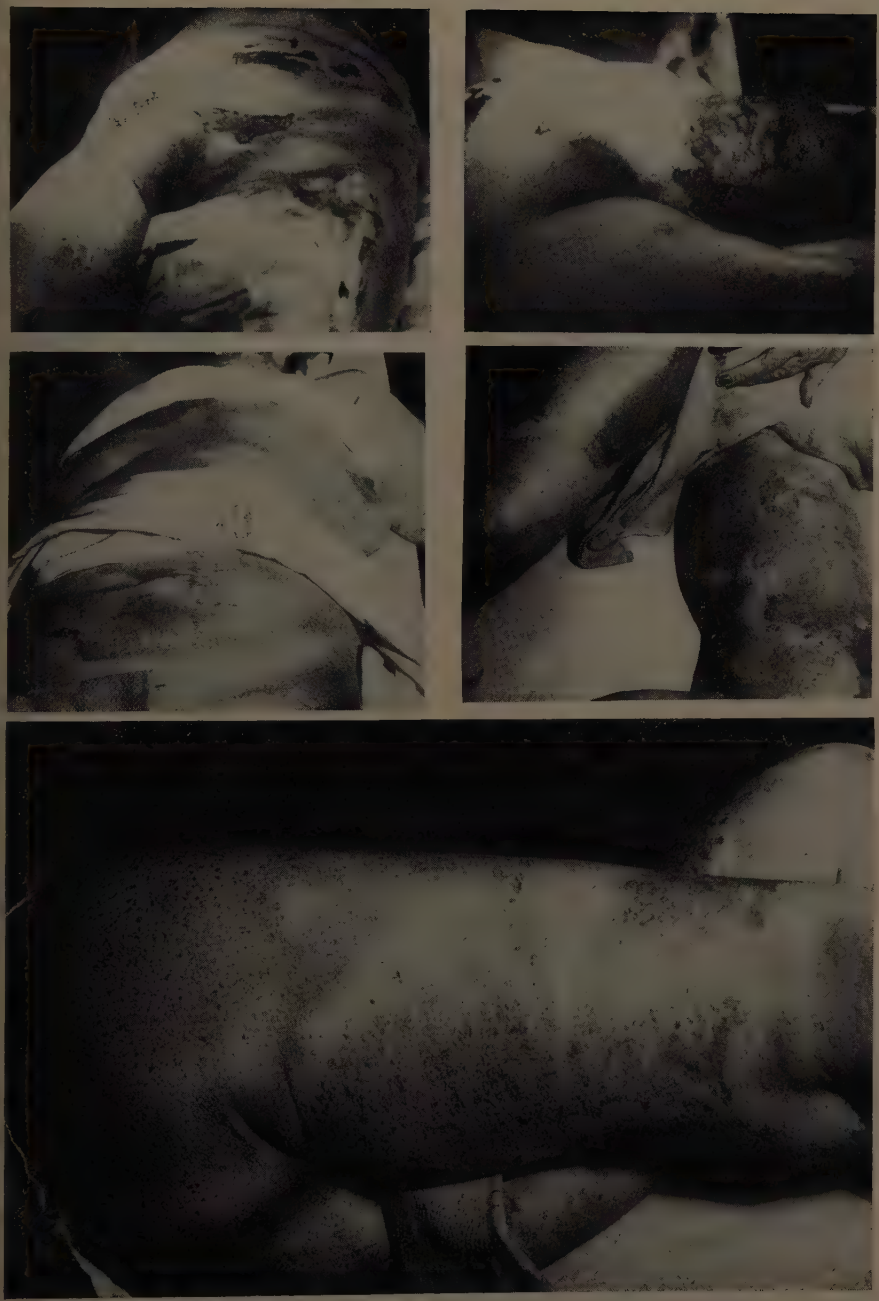
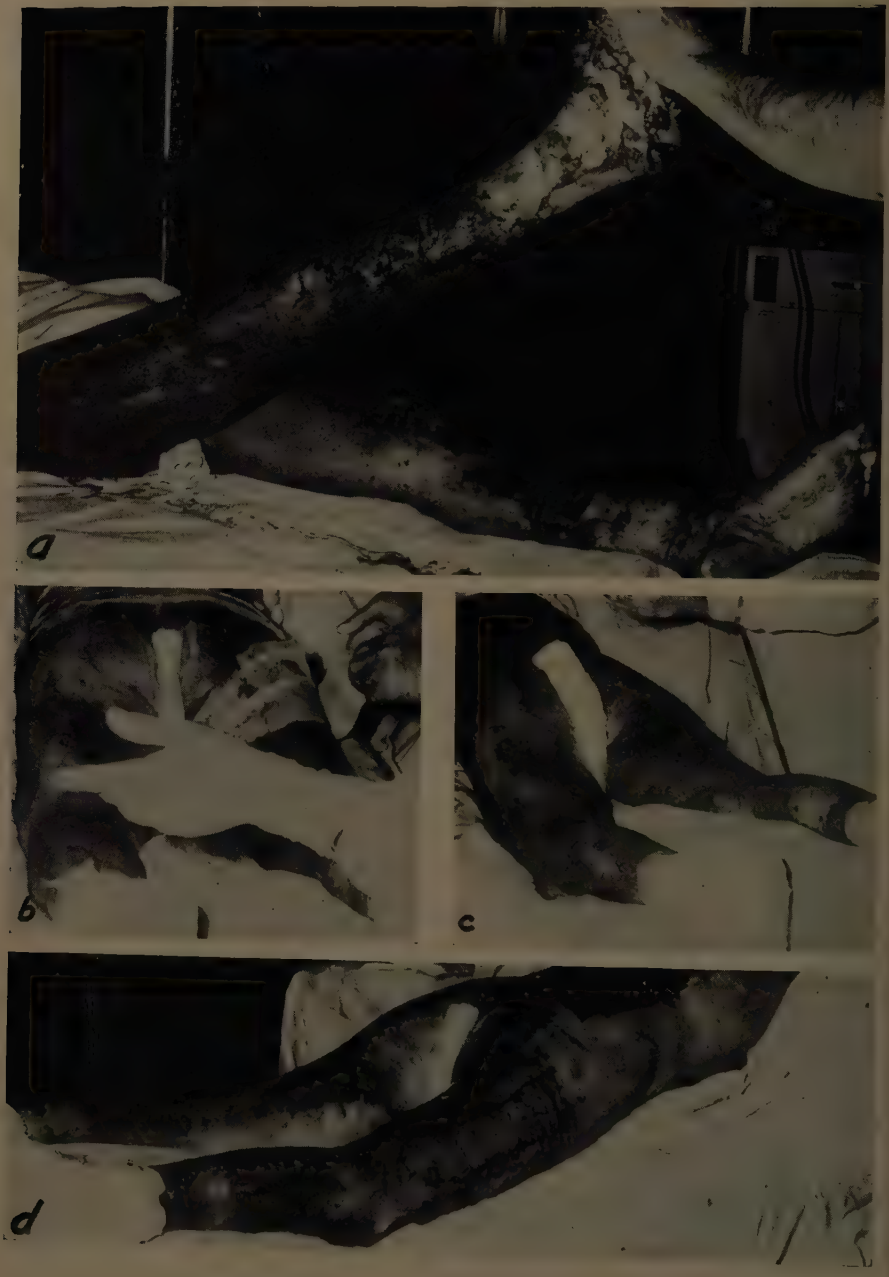
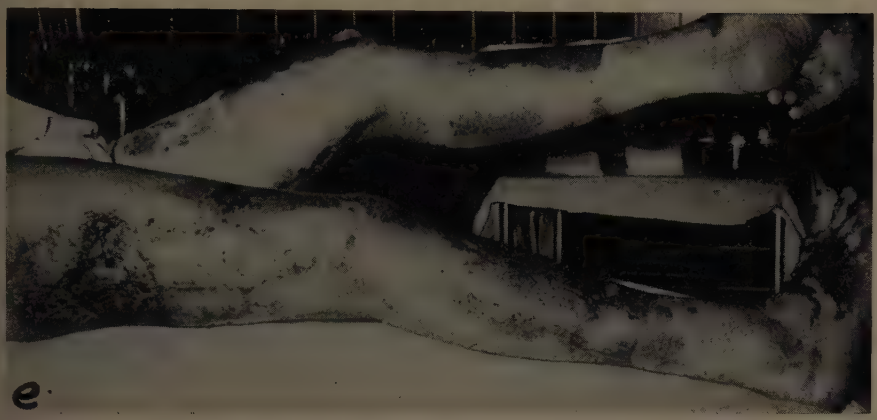


FIGURE 3. (*a*) Second- and third-degree burns of abdomen, thighs, and mammary region 16 days after burn trauma; suppurative eschar present. (*b*) Third degree burns of thigh infected with eschar 16 days after burn trauma. (*c*) Spontaneous healing of abdomen and mammary region 24 days after debridement and daily Triburon dressings. (*d*) Healing of thigh burn after debridement and daily Triburon dressings and skin grafts. (*e*) Thigh wound healing after debridement and daily Triburon dressings and skin grafts.


a
b
c
d



wounds were dressed with Triburon daily for 3 days in preparation for skin grafting. No infection or suppuration occurred.

Case 10. A 34-year-old male sustained second- and third-degree burns of approximately 45 per cent of body surface. He was seen 6 months later with isolated unhealed burn areas of the abdomen, back, thighs, and legs. Triburon was applied daily for 2 weeks. This drug seemed to be most effective in comparison with other drugs used previously.

Discussion

From the present series, it is evident that Triburon was highly effective in controlling infection and preventing contamination in all 10 cases without delaying wound healing. While it is difficult to estimate how soon healing would have occurred without the use of Triburon, it is significant that some burns initially thought to be of full thickness and to require many skin grafts remained free of infection and healed spontaneously. In addition, it was felt that grafting, when required, could be performed earlier than had been originally anticipated from the extent and severity of the wound. In one case successful grafting was possible 5 days after treatment with Triburon was instituted. One patient with second-degree burns treated on an outpatient basis showed complete healing within 2 weeks. None of the patients showed any evidence of irritation, sensitization, or systemic side effects, although large amounts of the ointment were frequently applied. Besides the drug's clinical efficacy and safety, its ease of application—an important factor in reducing nursing care and time—has impressed us. Moreover, in contrast to previously used preparations, the Triburon dressings could easily be peeled away from epithelialized wounds without disturbing the new tissue.

FIGURE 4. (*a*) Third-degree burns of both legs with eschar formation 3 days after burn. (*b*) Debridement and application of Triburon-impregnated fine mesh gauze to burn under anesthesia. (*c*) Wound ready to accept skin graft after application of Triburon and prior to application of split-thickness skin grafts. (*d*) Split-thickness skin grafts applied to burn areas of both thighs and legs. Triburon gauze applied to grafted areas and donor sites. (*e*) Successful "take" of split-thickness skin graft to thighs and legs.

Summary

Triclobisonium chloride was used in a series of 10 patients with early and late burn wounds of both a minor and critical nature. The ointment was applied on fine-mesh gauze to the entire burn surface and to all graft donor sites. In all donor sites regeneration resulted without delay.

No suppuration or reinfection was noted in any of the patients treated.

Irritation, sensitization, and adverse systemic reactions were not observed, despite the fact that as much as 45 per cent of body surface was treated with the ointment.

The clinical impression was that Triburon may have permitted earlier grafting and that areas that might otherwise have required grafting healed spontaneously.

Triburon merits further evaluation in the routine topical treatment of burn wounds by virtue of the successful results of this series.

Acknowledgment

I wish to give grateful acknowledgment to Ralph M. L. Buchanan, Medical Director of the Ingersoll-Rand Co., New York, N. Y., and to the company for their generous help and courteous cooperation in this study.

Discussion

D. McCullagh Mayer (*New York Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y.*): There are two fundamental problems in the management of acute burns: (1) The prevention or treatment of shock, or both, and (2) the prevention of infection.

In my experience I have seen and treated acute burns with perhaps every type of treatment. Prior to World War II the favored agent was tannic acid. Every fire truck in the city of New York carried bottles of tannic acid for immediate application. I understand that ships of the United States Navy had similar facilities. As internes and residents we saw the horrible results of this treatment, which resulted in most cases in gross infection. Later the various dyes and ointments were emphasized, with somewhat better results. Just prior to and during World War II pressure dressings were in vogue. Results were again somewhat better; however, I believe the reason for this was not the pressure dressing per se, but rather the fact that the burns were being debrided under aseptic conditions, thus preventing infection. The supposed advantage of the pressure dressing was that it prevented fluid loss; this has been disproven. At any rate, it did at least help to prevent infection.

After World War II the exposure method gained considerable favor; it has advantages and advocates. At first, antibiotics were applied to the burned surface. Now it is believed by most observers that there is little value in the topical application of antibiotics to the burn proper.

In the exposure method, burns are debrided again under aseptic conditions, and the wound is protected by sterile sheets and drapes. A coagulum is permitted to form that acts as a temporary covering. However, this does not obviate the necessity for skin grafting of third-degree burns at a later time. Here again, infection has been prevented by proper burn asepsis.

As in so many controversial problems in medicine and surgery there is no agreement concerning the management of burns. The very fact that so much has been written and so many agents have been used in the care of burns is an indication that there is no single ideal method.

Advances have been made in the treatment of burns but, in my opinion, more benefit has come from the prevention of infection, by whatever method, than from any single type of treatment.

This raises the problem of how best to prevent infection. Certainly, aseptic debridement is mandatory. After debridement the surgeon must decide whether he is to employ the occlusive or the exposure method. If the occlusive method is used, what should be placed on dressings to help prevent infection? Certainly Vaseline gauze is not the answer since, as most surgeons agree, Vaseline gauze may macerate tissue. If the exposure method is decided upon, this must be attended by many favorable conditions. It has its limitations in young children, who may contaminate their wounds, and it is not favorable in circumferential burns. Therefore, we must consider the use of some topical medication, of which there are many.

It would be impossible to name one certain medication that would be, in all cases, superior to all others.

My associate and I have been using Triburon* ointment for the past several months. We have used it as initial therapy when we have had the good fortune to see the burned patient first, and we have also used it on infected burns. We believe it has great merit and have had no complications, such as sensitivity, from its use.

Finally, I would like to emphasize again the importance of the prevention of infection in burns. A second-degree burn without infection will go on to complete healing; a second-degree burn, once infected, becomes a third-degree burn. An infected third-degree burn may be a matter of life or death. The infected-burn patient soon becomes a serious medical problem because of protein loss, secondary anemia, and general debility.

When the donor site becomes infected after skin grafting, the problem becomes complicated. When a person is burned, it is not always possible to determine the degree. If the entire burned area can be kept clean, the areas of second-degree burn will become delineated and heal, while the third-degree areas will be clean and ready for grafting. Any agent that helps achieve this must be acceptable to the profession. There is definite indication for the use of a bacteriostatic ointment in the treatment of burns.

* Hoffmann-La Roche.

LOCAL THERAPY IN VAGINITIS

Nejdat Mulla and John J. McDonough
St. Elizabeth Hospital, Youngstown, Ohio

Vaginitis, the most common disease of the female genital tract, presents a challenge to every physician treating women. The infecting organisms almost regularly encountered are *Trichomonas vaginalis*, *Candida albicans*, and *Hemophilus vaginalis*.

T. vaginalis, described in 1836 by Donne, is accepted as the primary nonbacterial cause of vaginitis. Its prevalence in the American female, including asymptomatic carriers, is estimated at 30 per cent.[1, 2] Predominating during the child-bearing years,[3] it is manifest from the period of infancy[4] to beyond the menopause.[5]

C. albicans has been reported as the only pathogenic species of mycosis found in the vagina and isolated from the stools.[6] Its prevalence is estimated at 20 per cent. However, only 38 per cent of the patients harboring *Monilia* exhibit signs and symptoms.[7] The diagnosis of increasing numbers of *Monilia* infections concomitant with the widespread use of antibiotics has opened a new field in broad-spectrum and antimonilial preparations.

Hemophilus vaginalis has been described as the causative agent of nonspecific vaginitis. However, the etiological aspects of this organism recently have aroused some controversy in the literature. Gardner and Dukes,[8] as well as others[9] have attempted to describe and classify the organism. Some investigators[10] deny its existence as a single entity and question its assumed pathogenic role. Our examination of the vaginal flora of 43 asymptomatic, nonpregnant women between the ages of 30 and 45 yielded the following results. Sixty per cent of the patients harbored *H. vaginalis*, *T. vaginalis*, or *C. albicans*; these were always found in association with other microorganisms. Similar findings have been reported by several investigators.[11, 12]

Successful treatment is difficult because of the persistent recurrence of vaginitis in all age groups. While reinfection from the marital partner is, undoubtedly, a factor, Kessel and Thompson[13] showed that the *Trichomonas* live in the dried state outside the vagina for as long as 8 hours. Most of the available therapeutic preparations are effective *in vitro*, but fail to eradicate the organism in the infected patient. Triburon (triclobisonium chloride), a topical agent in a 0.1 per cent concentration in a Carbowax base, has met with greater success in our experience than any of the newer preparations against *Trichomonas* and mixed infections.

Materials, Diagnosis, and Therapy

Thirty-two private and 41 clinic patients, between 8 and 54 years of age, from the Department of Obstetrics and Gynecology of St. Elizabeth Hospital, who presented themselves for treatment of an irritating vaginal discharge, make up the basis of this report. Sixteen of the 73 patients were pregnant, and six of the non-pregnant women manifested eroded cervices. Most of these patients had been treated previously with available bacteriostatic agents.

Diagnosis of vaginitis was based upon symptoms, clinical findings, microscopic wet smears, and microbiological examinations of the material taken from the posterior fornix of the vagina (TABLE 1).

T. vaginalis was isolated in 26 (45.6 per cent) nonpregnant and in 5 (31.2 per cent) pregnant women. *C. albicans* was found in 14 (24.5 per cent) nonpregnant and in 6 (37.5 per cent) pregnant women. Small Gram-negative bacilli conforming to the description of *H. vaginalis* were isolated in only 13 (22.8 per cent) nonpregnant patients. These were usually isolated in conjunction with one or more of the following microorganisms: *Escherichia coli*, nonhemolytic *Streptococcus*, alpha and beta *Streptococcus*, *Proteus vulgaris*, *Staphylococcus albus*, *Staphylococcus aureus*, *Lactobacillus* and *Pseudomonas aeruginosa.*

After establishment of a diagnosis, the vulva and vagina were cleansed of discharge with a mild detergent and dried with cotton balls. One full applica-

TABLE 1

ORGANISMS FOUND IN THE VAGINA IN 43 ASYMPTOMATIC AND 73 SYMPTOMATIC PATIENTS

Organisms	Asymptomatic		Symptomatic			
	Nonpregnant		Nonpregnant		Pregnant	
	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage
Trichomonas	8	18.5	26	45.6	5	31.2
Monilia	9	21	14	24.5	6	37.5
H. vaginalis	9	21	13	22.8	—	—
E. coli	5	11.5	17	29.8	6	37.5
Nonhemolytic *streptococcus*	5	11.5	5	8.7	2	12.5
Alpha *streptococcus*	8	18.5	10	17.5	1	6.2
Beta *streptococcus*	7	16.2	14	24.5	2	12.5
Proteus vulgaris	2	4.6	6	10.5	1	6.2
Staph. albus	18	42	19	33.3	—	—
Staph. aureus	1	2.3	3	5.2	—	—
Lactobacillus	10	23.2	11	19.2	—	—
P. aeruginosa	—	—	3	5.2	—	—

tor of Triburon ointment was then inserted into the vagina. A large cotton ball was placed between the labia to prevent escape of the ointment and discomfort due to exuding moisture.

In order to avoid contamination of the vulva and perineum with discharge material, it was advised that a cotton ball be used between the labia throughout treatment and changed frequently. The use of perineal pads was discouraged, except for placement over the cotton when necessary to ensure the patient's sense of security. This procedure also was advocated during the menstrual period for the purpose of inhibiting dissemination of microorganisms from the decomposed, infected menstrual material occurring on the pad.

The patient was instructed to use a vinegar vaginal douche daily and to insert one full applicator of the ointment into the vagina each night before retiring. We recommended the rubbing of a small amount of ointment over the vulva and perineum at intervals during the day, particularly after voiding.

Evaluation was made at the end of the second week of treatment, the patient

having been directed to refrain from the use of the medication and douche 2 days prior to the visit. Therapy was carried out for a period of 4 weeks and for 3 days following the next 3 menstrual periods.

Side Effects

Only 2 of 73 patients treated with Triburon ointment complained of a burning sensation in the vagina. This was relieved upon discontinuance of the medication for 3 days and substitution of an alkaline for an acid douche. Thereafter, the patients resumed the prescribed treatment without further discomfort. The ointment was tolerated well both in the vagina and on the vulvar region.

Results

Sixty-seven patients were relieved of discharge, itching, and burning sensation after 3 or 4 applications of Triburon ointment. When, at the end of 2 to 3 weeks, clinical and microscopic examinations were negative, these 67 women

TABLE 2
RESULTS AFTER 2 TO 3 WEEKS TREATMENT WITH TRIBURON

	No. of patients	Percentage
Cleared symptomatically	67	91.7
Improved symptomatically	6	8.3
Total	73	100
Negative cultures	61	83.5
Positive cultures*	12	16.4
Total	73	99.9

* Positive only for *Candida albicans*.

(91.7 per cent) were considered to be cleared completely (TABLE 2). Fifty-one of the above group have now been followed for a period of not less than 3 months and have remained free of symptoms. Bacteriological examinations revealed the presence of only *Lactobacillus* and normal vaginal mucosa. The 16 remaining patients are still under observation.

The 2 patients who developed vaginal burning sensation and in whom therapy was interrupted for a period of 3 days were free of symptoms, with negative clinical findings, after 3 weeks of resumption of treatment. However, cultures disclosed the presence of *C. albicans*. This organism was isolated, also, in 4 patients listed as improved.

One patient, presenting a severely inflamed, granulated, vaginal mucosa with a purulent discharge due to *Pseudomonas*, improved within 3 weeks. Bacteriological examination is negative and the vaginal mucosa is returning to normal. The patient is still under treatment.

The 16 pregnant women responded well to therapy. Triburon was used immediately *post partum* on 6 women. Neither recurrence nor untoward reaction was noted in either mother or infant. Four women listed as improved

are still being treated. Cervical erosion healed completely in 4 cases and greatly improved in 2.

Discussion

Normal vaginal epithelium will not produce vaginitis, even when trichomonads are harbored in the male urethra and spread by sexual intercourse. However, factors that disturb the vaginal epithelium, such as bloody discharge, change in vaginal secretions, diminution in glycogen, or a mixture of cocci with bacilli and saprophytes, render it susceptible to vaginitis. In our study of asymptomatic patients, we found 18.5 per cent harboring the organism in the absence of symptoms and clinical findings. Therefore, despite the potency of the trichomonacide, the vaginal mucosa must be restored to normal if therapy is to achieve favorable results.

Helms[14] reported that X-ray studies indicated the advantages of a jelly over insufflations, tablets, or suppositories because a jelly spreads faster and is retained longer. The evidence accumulated in our investigation indicates definite advantages of Triburon over preparations presently available. Its high antibacterial and antitrichomonal activity *in vivo*, as well as rapidity of diffusion and prolonged retention, seem to promote its efficacy and restore the vaginal epithelium to a normal state. The elimination of pathogenic organisms from the vagina appears to reduce symptoms of cystitis in the female patient.

References

1. Buxton, L. & D. Weinman. 1957. *In* Progress in Gynecology. **3:** 387. J. Z. Meigs & S. H. Sturgis, Eds. Grune & Stratton. New York.
2. Lammert, A. C. 1958. Diagnosis and treatment of vaginitis. Postgrad. Med. **23:** 280.
3. Jones, C. P., B. Carter, W. L. Thomas, R. A. Ross & R. N. Creadick. 1947. Mycotic vulvovaginitis and the vaginal fungi. A report of 280 patients. Am. J. Obstet. Gynecol. **54:** 738.
4. Kotcher, E., K. Keller & L. A. Gray. 1958. A microbiological study of pediatric vaginitis. J. Pediat. **53:** 210.
5. Feo, L. G. 1956. *Trichomonas vaginalis* infection in postmenopausal women. Am. J. Obstet. Gynecol. **72:** 1335.
6. Conant, N. F., D. T. Smith, R. D. Baker, J. R. Callaway & D. S. Martin. 1954. Manual of Clinical Mycology. : 456. Saunders. Philadelphia, Pa.
7. Campbell, R. M. & M. H. Parrott. 1950. Vulvovaginal moniliasis. Am. J. Obstet. Gynecol. **59:** 1005.
8. Gardner, H. L. & C. D. Dukes. 1955. *Haemophilus vaginalis* vaginitis. Am. J. Obstet. Gynecol. **69:** 962.
9. Deming, J. E. 1955. *Haemophilus influenzae* vaginitis. Northwest Med. **54:** 992.
10. Brewer, J. I., B. Halpern & G. Thomas. 1957. *Hemophilus vaginalis* vaginitis. Am. J. Obstet. Gynecol. **74:** 834.
11. Hunter, C. A. & K. R. Long. 1958. A study of microbiological flora of the vagina. Am. J. Obstet. Gynecol. **75:** 865.
12. Heltai, A. & P. Teleghany. 1959. Nonspecific vaginal infection. A critical evaluation of *Hemophilus vaginalis*. Am. J. Obstet. Gynecol. **77:** 144.
13. Kessel, J. F. & C. F. Thompson. 1950. Survival of *Trichomonas vaginalis*. A laboratory and clinical study. Proc. Soc. Exptl. Biol. Med. **74:** 755.
14. Helms, W. C. 1953. Leukorrhea. J. Med. Assoc. Georgia. **42:** 367.

LOCAL THERAPY IN VAGINITIS: EXPERIENCE WITH A NEW ANTIBACTERIAL AGENT

Lewis E. Savel, David B. Gershenfeld, Jerrold Finkel, Paul Drucker
Department of Obstetrics and Gynecology, Beth Israel Hospital, Newark, N. J.

Vaginitis, a recurrent problem in many patients, is common in every gynecologist's practice. In recent years numerous new therapeutic agents have been developed for the treatment of the various types of vaginitis. Claims of specificity for one or another type have been made, but clinical therapeutic results have been neither specific nor dramatic. The study reported in this paper is a clinical evaluation of a new antibacterial ointment (Triburon*) in the treatment of vaginitis.

Triburon chloride is a bisquaternary compound (triclobisonium chloride) of low systemic toxicity and high bacteriostatic and moderate bactericidal activity against Gram-positive and Gram-negative organisms. *In vitro*, Triburon was found to inhibit the growth of *Trichomonas vaginalis* and to be effective in suppressing the growth of *Candida albicans*.[1] Topical applications of Triburon on the skin caused no local reaction.[2, 3] In our study an ointment in Carbowax (0.1 per cent) was used.

Materials and Methods

The medication was administered to 90 private† and clinic‡ patients, but follow-up was accomplished on only 55. These 55 patients are those on whom this report is based.

The diagnosis of all patients with vaginitis (pruritus or leukorrhea, or both) was made solely on laboratory examination. At the first visit a clean vaginal speculum was inserted and a specimen of the discharge was obtained. The discharge was examined initially by the hanging-drop method. If no *Trichomonas* was found on the hanging drop, if a suggestion of *Monilia* was noted, or if the hanging drop failed to show either of these, culture on Nickerson's medium was begun and the cultures read at the end of seven days.

Classification of the vaginitis was made as follows: (1) monilial vaginitis if the Nickerson's culture was positive, regardless of the presence or absence of *Monilia* in the hanging drop; (2) trichomonal vaginitis if the hanging drop showed definite *Trichomonas*; (3) nonspecific vaginitis if the hanging drop was not diagnostic of either *Trichomonas* or *Monilia* and the culture (Nickerson's) was negative.

All patients were given tubes of Triburon ointment with vaginal instillers. They were instructed to instill the ointment (5 gm.) into the vagina in the morning and at bedtime for 2 weeks. No douching was allowed during the course of therapy. Patients were requested to report their progress after 1 and 2 weeks' therapy. The treatment was continued for 2 weeks regardless of the subjective report made at the end of the first week. If a menstrual

* Hoffmann-La Roche.
† From the office of L.E.S. and D.B.G.
‡ From the gynecology clinic of Beth Israel Hospital, Newark, N. J.

period occurred during the treatment, the instillations were continued despite vaginal bleeding. Patients were asked to report any recurrence of symptoms after the initial 2 weeks' therapy. A second course of medication (for 2 weeks) was given if complete relief of pruritus and leukorrhea was not obtained after the first 2 weeks' treatment.

Improvement was judged by the absence of pruritus and decrease in the amount of leukorrhea. Complete absence of leukorrhea did not occur, because the liquefaction of the ointment contributed to the vaginal discharge.

Results

In the monilial vaginitis group (TABLE 1), treatment and follow-up were given to 19 private and 10 clinic patients. Of the private nonpregnant pa-

TABLE 1
MONILIAL VAGINITIS

	Total patients		No. of patients improved		No. of patients not improved	
	Private	Clinic	Private	Clinic	Private	Clinic
Pregnant	1	3	0	1	1	2
Nonpregnant	18	7	15	4	3	3
Total	29		20		9	

TABLE 2
TRICHOMONAL VAGINITIS

	Total patients		No. of patients improved		No. of patients not improved	
	Private	Clinic	Private	Clinic	Private	Clinic
Pregnant	2	0	2	—	0	—
Nonpregnant	7	1	6	1	1	0
Total	10		9		1	

tients, 15 of 18 (83.33 per cent) were improved after the first 2 weeks of treatment. The 1 pregnant patient in this group was subjectively unimproved and had persistently positive Nickerson's culture after the 2 weeks' initial therapy. A second 2-week course of treatment in this patient was ineffective. Among the clinic patients, after 2 weeks' treatment, 4 of 7 nonpregnant women were improved (57.14 per cent) and 1 of 3 pregnant women improved (33.33 per cent). Thus, 20 of the 29 patients (68.97 per cent) in this group with monilial vaginitis were improved after 2 weeks' therapy with Triburon. No second course of therapy was given to the clinic patients because they failed to return.

Trichomonal vaginitis was treated in 9 private patients and 4 clinic patients. Only one of the latter returned, reporting complete absence of symptoms after the initial therapy (TABLE 2). Of the 9 private patients (2 pregnant), 8 (88.88

per cent) were completely relieved after the initial 2 weeks' therapy with Triburon. The 1 unimproved patient received a second 2 weeks' therapy and then was symptom-free. Thus, 9 of 10 patients (90 per cent) treated for trichomonal vaginitis were improved after the initial therapy.

Nonspecific vaginitis was treated in 12 private patients, 2 of whom were pregnant (TABLE 3), with complete relief in 10 (83.33 per cent) after the first 2 weeks' treatment. The other 2 were completely relieved after a second 2 weeks' therapeutic course. Four clinic patients were treated for nonspecific vaginitis and 3 (75 per cent) were improved with the 2 weeks' therapy. Thus, 13 of 16 patients (81.25 per cent) with nonspecific vaginitis were improved after the first course of therapy.

TABLE 3
NONSPECIFIC VAGINITIS

	Total patients		No. of patients improved		No. of patients not improved	
	Private	Clinic	Private	Clinic	Private	Clinic
Pregnant	2	0	2	—	0	—
Nonpregnant	10	4	8	3	2	1
Total	16		13		3	

TABLE 4
RECURRENCE OF VAGINITIS

Type of vaginitis	No. of patients with recurrence	Percentage of initially improved patients
Monilial	8	53.3
Trichomonal	2	25.0
Nonspecific	1	10.0

Recurrence of the monilial vaginitis was found within 3 to 90 days in 8 of the 15 private patients (53.33 per cent) who were initially improved (TABLE 4). Symptoms had returned and Nickerson's cultures were positive. Five of these 8 patients with a recurrence accepted a second 2 weeks' treatment with Triburon: 3 improved, 1 had no response, and 1 had a second recurrence 30 days after the second course of medication. Thus, 10 of the 15 private patients (66.66 per cent) with monilial vaginitis remained improved.

Trichomonal vaginitis recurred in 2 of the 8 private patients (25 per cent) who had been improved with the initial 2 weeks' Triburon therapy (TABLE 4). One showed recurrence in 1 week and one in 3 weeks. Both patients received a second weeks' course of medication and were relieved.

Nonspecific vaginitis recurred in 1 of the 10 private patients (10 per cent) who had initially improved (TABLE 4). This recurrence was 6 months after the initial therapy and was unresponsive to a second 2 weeks' course of therapy.

Discussion

The treatment of vaginitis in the physician's office is a perplexing problem. The search for a single therapeutic agent that will be curative in all varieties of vaginitis has not been rewarding. The hope for complete control must depend on effective local treatment in the female, together with an effective therapy (local or oral) in the male.

Symptomatic treatment of vaginitis without identification of a specific infesting or infecting organism is fruitless. Specific identification of the pathogenic organism must be made.

The treatment of vaginitis with Triburon ointment (0.1 per cent) instillations into the vagina was most successful in the trichomonal and nonspecific vaginitis. Monilial vaginitis was most resistant to treatment and recurred most often after this therapy.

The patients generally accepted the ointment therapy well. There was some leakage of the ointment, which made evaluation of leukorrhea difficult, since the patients were unable to decide whether the vaginal discharge was leukorrhea or liquefied ointment.

It was difficult to be certain that the proper amount of ointment (5 gm.) was actually instilled into the vagina at each home treatment. This uncertainty was a disadvantage in the therapy. Numerous patients volunteered the opinion that previous vaginal therapy with tablets had been more acceptable and easier to manage. Moreover, tablet therapy makes the dosage administered more certain.

Summary

A plan of therapy for vaginitis with a new ointment (Triburon, 0.1 per cent) has been described.

Trichomonal vaginitis responded best to Triburon therapy (90 per cent); the nonspecific type responded next best (81.25 per cent); and monilial vaginitis responded least (68.97 per cent).

Recurrence was highest for monilial vaginitis (53.3 per cent) and low for trichomonal (25 per cent) and nonspecific vaginitis (10 per cent) after Triburon therapy.

Triburon ointment therapy was found to be effective local therapy for trichomonal and nonspecific vaginitis and was well accepted by the patients.

References

1. Schnitzer, R. J., E. Grunberg, W. F. DeLorenzo & R. E. Bagdon. Triburon, an antimicrobial agent with local activity in living host tissues. Antibiotics & Chemotherapy. In press.
2. Edelson, E., E. Grunberg & T. V. Morton. 1959. Clinical appraisal of a new topical quaternary compound Ro 5-0810/1. Antibiotics Ann. 1958–1959. : **110.**
3. Robinson, R. D. V. & L. E. Harmon. 1959. Local application of triclobisonium chloride in the treatment of pyogenic dermatoses. Antibiotics Ann. 1958–1959. : **113.**

Discussion

Robert Turell (*Mt. Sinai Hospital and Albert Einstein College of Medicine, New York, N. Y.*): Recently, a 0.1 per cent concentration of a new compound,

N,N′-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N′-dimethyl-1,6-hexanediamine bis(methochloride)hemihydrate (Triburon*) in a Carbowax base was accorded a clinical trial in the care of clean as well as infected surgical anorectal wounds. In 25 hemorrhoidectomies, compared with 25 controls, this substance neither expedited nor interfered with the healing of the wounds. Following drainage and unroofing of periano-perirectal abscesses in 23 patients and of sacrococcygeal suppurations in 7 patients, the topical use of this substance resulted in cleaner-appearing wounds without appreciably shortening the time for effective healing. The same was observed in the healing of the wounds following fistulectomy and fissurectomy in 12 and 29 patients, respectively.

Impregnated in gauze, this substance has thus far been used with satisfaction in the perineal wounds and about the abdominal colostomy stoma following abdominoperineal resection of the rectum in three cases. Work on this project is progressing.

To date, hypersensitivity reactions, which are usual with the use of new drugs, have not been encountered in this group of surgically treated patients, some with wounds with large raw or vascular areas. Furthermore, there have been no untoward local or systemic reactions in 31 patients with perianal cutaneous bacterial infections such as (pyoderma, furunculosis, and folliculitis) with or without associated pruritus, in 5 persons with monilial, and in 12 individuals with antibiotic (staphylococcal) pruritus in which this new therapeutic agent appeared effective.

This new substance also appears to be a good lubricant for postoperative anal explorations and may be used as a safe substitute for the still widely used anesthetic drugs that may cause local deleterious effects in many cases.

Three patients with anal pruritus, in whom the topical application of either steroid hormones or Triburon was poorly effective, responded to a combination of 0.1 per cent Triburon chloride and 0.5 per cent of hydrocortisone. The problem of potentiation of these two substances remains to be assessed.

* Hoffmann-La Roche.

Printed in the United States of America

MONOGRAPHIC PUBLICATIONS
OF
THE NEW YORK ACADEMY OF SCIENCES

(LYCEUM OF NATURAL HISTORY, 1817–1876)

(1) The ANNALS (octavo series), established in 1823, contain the scientific contributions and reports of researches, together with the records of meetings of the Academy. The articles that comprise each volume are printed separately, each in its own cover, and are distributed immediately upon publication. The prices of the separate articles depend upon their length and the number of illustrations, and may be ascertained upon application to the Executive Director of the Academy.

Current numbers of the ANNALS are sent free to all Members of the Academy desiring them.

(2) The SPECIAL PUBLICATIONS, established in 1939, are issued at irregular intervals as clothbound volumes. The price of each volume will be advertised at time of issue.

(3) The MEMOIRS (quarto series), established in 1895, are issued at irregular intervals. It is intended that each volume shall be devoted to monographs relating to some particular department of science. Volume I, Part 1 is devoted to Astronomical Memoirs, Volume II to Zoological Memoirs. No more parts of the Memoirs have been published to date. The price is one dollar per part.

(4) The SCIENTIFIC SURVEY OF PORTO RICO AND THE VIRGIN ISLANDS (octavo series), established in 1919, gives the detailed reports of the anthropological, botanical, geological, paleontological, zoological, and meteorological surveys of these islands.

Subscriptions and inquiries concerning current and back numbers of any of the publications of the Academy should be addressed to

EXECUTIVE DIRECTOR

The New York Academy of Sciences
2 East Sixty-third Street
New York 21, N. Y.